KAR 05-28-02

L2 ANSWER 1 OF 51 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:256519 CAPLUS
DOCUMENT NUMBER: 136:304039
TITLE: Antisense modulation of **MEKK4** expression
INVENTOR(S): Ward, Donna T.; Gaarde, William A.; Monia, Brett P.; Wyatt, Jacqueline R.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002027033	A1	20020404	WO 2001-US30549	20010928

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-676436 A 20000929
AB Antisense compds., compns. and methods are provided for modulating the expression of **MEKK4**. The compns. comprise antisense compds., particularly antisense oligonucleotides, targeted to nucleic acids encoding **MEKK4**. Methods of using these compds. for modulation of **MEKK4** expression and for treatment of diseases assocd. with expression of **MEKK4** are provided.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L2 ANSWER 2 OF 51 USPATFULL
ACCESSION NUMBER: 2002:105925 USPATFULL
TITLE: Method and product for regulating apoptosis
INVENTOR(S): Johnson, Gary L., Boulder, CO, UNITED STATES
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002055130	A1	20020509
APPLICATION INFO.:	US 2001-858754	A1	20010516 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-23130, filed on 13 Feb 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-39740P	19970214 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS: 39

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Page(s)
LINE COUNT: 6845
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to isolated MEKK1 proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods to use such proteins to regulate apoptosis. The invention provides active fragments of MEKK1 proteins that are generated upon cleavage of MEKK1 with a caspase protease. These active fragments are capable of stimulating apoptosis. Moreover, the invention provides protease-resistant forms of MEKK1 proteins, that are resistant to cleavage by caspase proteases and that are capable of inhibiting apoptosis. Still further, the invention provides methods for generating an active fragment of MEKK1, methods of identifying modulators of the apoptotic activity of an active fragment of MEKK1 and methods of identifying modulators of caspase-mediated cleavage of MEKK1.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 3 OF 51 USPATFULL
ACCESSION NUMBER: 2002:38558 USPATFULL
TITLE: Expressed sequences of arabidopsis thaliana
INVENTOR(S): Gorlach, Jorn, Durham, NC, UNITED STATES
An, Yong-Qiang, San Diego, CA, UNITED STATES
Hamilton, Carol M., Apex, NC, UNITED STATES
Price, Jennifer L., Raleigh, NC, UNITED STATES
Raines, Tracy M., Durham, NC, UNITED STATES
Yu, Yang, Martinsville, NJ, UNITED STATES
Rameaka, Joshua G., Durham, NC, UNITED STATES
Page, Amy, Durham, NC, UNITED STATES
Mathew, Abraham V., Cary, NC, UNITED STATES
Ledford, Brooke L., Holly Springs, NC, UNITED STATES
Woessner, Jeffrey P., Hillsborough, NC, UNITED STATES
Haas, William David, Durham, NC, UNITED STATES
Garcia, Carlos A., Carrboro, NC, UNITED STATES
Kricker, Maja, Pittsboro, NC, UNITED STATES
Slater, Ted, Apex, NC, UNITED STATES
Davis, Keith R., Durham, NC, UNITED STATES
Allen, Keith, Cary, NC, UNITED STATES
Hoffman, Neil, Chapel Hill, NC, UNITED STATES
Hurban, Patrick, Raleigh, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002023280	A1	20020221
APPLICATION INFO.:	US 2001-770444	A1	20010126 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-178502P	20000127 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PARADIGM GENETICS, INC, 104 ALEXANDER DRIVE, BUILDING 2, P O BOX 14528, RTP, NC, 277094528
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
LINE COUNT: 3845
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Isolated nucleotide compositions and sequences are provided for Arabidopsis thaliana genes. The nucleic acid compositions find use in identifying homologous or related genes; in producing compositions that modulate the expression or function of its encoded protein, mapping functional regions of the protein; and in studying associated physiological pathways. The genetic sequences may also be used for the genetic manipulation of cells, particularly of plant cells. The encoded

gene products and modified organisms are useful for screening of biologically active agents, e.g. fungicides, insecticides, etc.; for elucidating biochemical pathways; and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 4 OF 51 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002096905 MEDLINE
DOCUMENT NUMBER: 21671319 PubMed ID: 11700306
TITLE: Expression of Galpha 13 (Q226L) induces P19 stem cells to primitive endoderm via MEKK1, 2, or 4.
AUTHOR: Wang Hsien-yu; Kanungo Jyotshnabala; Malbon Craig C
CORPORATE SOURCE: Department of Physiology & Biophysics, University Medical Center, State University of New York, Stony Brook, New York
11794-8661, USA.. wangh@pharm.sunysb.edu
CONTRACT NUMBER: DK30111 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Feb 1) 277 (5) 3530-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020206
Last Updated on STN: 20020420
Entered Medline: 20020228

AB Galpha13 mediates the ability of the morphogen retinoic acid to promote primitive endoderm formation from mouse P19 embryonal carcinoma stem cells, a process that includes the obligate activation of Jun N-terminal kinase. Expression of the constitutively activated (Q226L) GTPase-deficient form of Galpha13 mimics retinoic acid and was used to investigate the signaling upstream of primitive endoderm formation. Jun N-terminal kinase 1 activity, MEK1,2, MKK4, and MEKK1 were constitutively activated in clones stably transfected to express Q226L Galpha13. Dominant negative forms of MEKK1 and **MEKK4** were expressed stably in the clones harboring Q226L Galpha13. Expression of dominant negative versions of either MEKK1 or **MEKK4** effectively blocks both the activation of Jun N-terminal kinase as well as the formation of primitive endoderm. Depletion of MEKK1, -2, or -4 by antisense oligodeoxynucleotides suppressed signaling from Q226L Galpha13 to JNK1 and primitive endoderm formation. We demonstrate that the signal linkage map from Galpha13 activation to primitive endoderm formation in these stem cells requires activation at three levels of the mitogen-activated protein kinase cascade: MEKK1, -2, or -4 for MAP kinase kinase kinase; MKK4 and/or MEK1 for MAP kinase kinase; and JNK1 for MAP kinase.

L2 ANSWER 5 OF 51 USPATFULL
ACCESSION NUMBER: 2001:229388 USPATFULL
TITLE: Expression monitoring of downstream genes in the BRCA1 pathway
INVENTOR(S): Oliner, Jonathan, Mountain View, CA, United States
Christians, Fred, Los Altos, CA, United States
Truong, Vivi, San Jose, CA, United States
Haber, Daniel, Chestnut Hill, MA, United States
Bean, James, Arlington, MA, United States
Miklos, David, W. Roxbury, MA, United States
Harkin, Denis Paul, Knockhill Park, Great Britain

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001051339	A1	20011213
APPLICATION INFO.:	US 2001-808352	A1	20010315 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-203677, filed on 1 Dec

1998, GRANTED, Pat. No. US 6258536
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, WASHINGTON, DC, 20001
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 2842
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Analysis of the genes whose expression is affected by BRCA1 has identified a set of genes, each of which is up- or down-regulated by BRCA1. Each of these genes, alone or in groups, can be used to determine the mutational status of a BRCA1 gene, to determine whether a particular allelic variant affects BRCA1 function, to diagnose neoplasia, and to help identify candidate drugs which may be useful as anti-neoplastic agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 6 OF 51 USPATFULL
ACCESSION NUMBER: 2001:235103 USPATFULL
TITLE: Method and product for regulating cell responsiveness to external signals
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6333170	B1	20011225
APPLICATION INFO.:	US 1996-628829		19960405 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-440421, filed on 12 May 1995, now abandoned Continuation-in-part of Ser. No. US 1994-323460, filed on 14 Oct 1994, now patented, Pat. No. US 5854043 Continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941 , said Ser. No. US 440421
Continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941 , said Ser. No. US 628829 Continuation-in-part of Ser. No. US 1995-410602, filed on 24 Mar 1995, now abandoned
Continuation-in-part of Ser. No. US 1995-472934, filed on 6 Jun 1995, now patented, Pat. No. US 5753446
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Kemmerer, Elizabeth
ASSISTANT EXAMINER: Basi, Nirmal S.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, DeConti, Jr., Esq., Guilio A., Lauro, Esq., Peter C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 40 Drawing Figure(s); 30 Drawing Page(s)
LINE COUNT: 6027
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to isolated MEKK proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods to use such proteins to regulate signal transduction in a cell. The present invention also includes therapeutic compositions comprising such proteins or nucleic acid molecules that encode such proteins and

their use to treat animals having medical disorders including cancer, inflammation, neurological disorders, autoimmune diseases, allergic reactions, and hormone-related diseases. When MEKK is expressed, it phosphorylates and activates MKKs 1-4 (also referred to as MEK-1, MEK-2 and JNKK1 and JNKK2).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 7 OF 51 USPATFULL

ACCESSION NUMBER:	2001:196837 USPATFULL			
TITLE:	Human MEKK proteins, corresponding nucleic acid molecules, and uses therefor			
INVENTOR(S):	Johnson, Gary L., Boulder, CO, United States			
PATENT ASSIGNEE(S):	National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6312934	B1	20011106	
	WO 9947686		19990923	
APPLICATION INFO.:	US 2000-423890		20000306	(9)
	WO 1999-US5556		19990315	
			20000306	PCT 371 date
			20000306	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	US 1998-78153P		19980316	(60)
	US 1998-99165P		19980904	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Prouty, Rebecca E.			
ASSISTANT EXAMINER:	Monshipouri, M.			
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP, Lauro, Esq, Peter C., Milasincic, Esq, Debra J.			
NUMBER OF CLAIMS:	29			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	35 Drawing Figure(s); 35 Drawing Page(s)			
LINE COUNT:	2856			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid molecules encoding human MEKK proteins, and isolated MEKK proteins, are provided. The invention further provides antisense nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and nonhuman transgenic animals carrying a human MEKK transgene. The invention further provides human MEKK fusion proteins and anti-human MEKK antibodies. Methods of using the human MEKK proteins and nucleic acid molecules of the invention are also disclosed, including methods for detecting human MEKK activity in a biological sample, methods of modulating human MEKK activity in a cell, and methods for identifying agents that modulate the activity of human MEKK.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 8 OF 51 USPATFULL

ACCESSION NUMBER:	2001:107621 USPATFULL
TITLE:	Expression monitoring of downstream genes in the BRCA1 pathway
INVENTOR(S):	Oliner, Jonathan, 173 Sierra Vista Ave., Unit 22, Mountain View, CA, United States 94043 Christians, Fred, 1444 Arbor Ave., Los Altos, CA, United States 94024 Truong, Vivi, 7082 Kindra Hill Dr., San Jose, CA, United States 95120 Haber, Daniel, 34 Monadonck Rd., Chestnut Hill, MA,

United States 02467
Bean, James, 9 Heath Rd., Arlington, MA, United States 02474
Miklos, David, 61 Oriole St., W. Roxbury, MA, United States 02132
Harkin, Denis Paul, 9 Knockhill Park, Belfast BT5 6HX, Northern Ireland, United Kingdom

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6258536	B1	20010710
APPLICATION INFO.:	US 1998-203677		19981201 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Fredman, Jeffrey
ASSISTANT EXAMINER: Chakrabarti, Arun K.
LEGAL REPRESENTATIVE: Banner & Witcoff, Ltd.
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 2762
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Analysis of the genes whose expression is affected by BRCA1 has identified a set of genes, each of which is up- or down-regulated by BRCA1. Each of these genes, alone or in groups, can be used to determine the mutational status of a BRCA1 gene, to determine whether a particular allelic variant affects BRCA1 function, to diagnose neoplasia, and to help identify candidate drugs which may be useful as anti-neoplastic agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 9 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:180630 BIOSIS
DOCUMENT NUMBER: PREV200200180630
TITLE: Phosphorylation is involved in the activation of metal-regulatory transcription factor 1 in response to metal ions.
AUTHOR(S): LaRochelle, Olivier; Gagne, Valery; Charron, Jean; Soh, Jae-Won; Seguin, Carl (1)
CORPORATE SOURCE: (1) Center de recherche en cancerologie, 11 cote du Palais, l'Hotel-Dieu de Quebec, Quebec, Quebec, G1R 2J6: Carl.Seguin@crhdq.ulaval.ca Canada
SOURCE: Journal of Biological Chemistry, (November 9, 2001) Vol. 276, No. 45, pp. 41879-41888. http://www.jbc.org/. print. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English

AB We have studied the role of phosphorylation in the activation of metal-regulatory transcription factor-1 (MTF-1) and metallothionein (MT) gene expression. We showed that MTF-1 is phosphorylated in vivo and that zinc stimulates MTF-1 phosphorylation 2-4-fold. Several kinase inhibitors were used to examine the possible involvement of kinase cascades in the activation of MTF-1. Metal-induced MT gene expression was abrogated by protein kinase C (PKC), c-Jun N-terminal kinase (JNK), phosphoinositide 3-kinase, and tyrosine-specific protein kinases inhibitors, as assayed by Northern analysis and by cotransfection experiments using a metal regulatory element-luciferase reporter plasmid. The extracellular signal-activated protein kinase and the p38 kinase cascades did not appear to be essential for the activation of MT gene transcription by metals. By using dominant-negative mutants of PKC, JNK, mitogen-activated kinase kinase 4 (MKK4), and MKK7, we provide further evidence supporting a role

for PKC and JNK in the activation of MTF-1 in response to metals. Notably, increased MTF-1 DNA binding in response to zinc and MTF-1 nuclear localization was not inhibited in cells preincubated with the different kinase inhibitors despite strong inhibition of MTF-1-mediated gene expression. This suggests that phosphorylation is essential for MTF-1 transactivation function. We hypothesize that metal-induced phosphorylation of MTF-1 is one of the primary events leading to increased MTF-1 activity. Thus, metal ions such as cadmium could activate MTF-1 and induce MT gene expression by stimulating one or several kinases in the MTF-1 signal transduction pathway.

L2 ANSWER 10 OF 51 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001553923 MEDLINE
DOCUMENT NUMBER: 21486459 PubMed ID: 11498536
TITLE: Oligomerization of human Gadd45a protein.
AUTHOR: Kovalsky O; Lung F D; Roller P P; Fornace A J Jr
CORPORATE SOURCE: NCI, National Institutes of Health, Gene Response Section, Bethesda, Maryland 20892, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Oct 19) 276 (42) 39330-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011016
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Gadd45a is an 18-kDa acidic protein that is induced by genotoxic and certain other cellular stresses. The exact function of this protein is not known. However, there is evidence for its involvement in growth control, maintenance of genomic stability, DNA repair, cell cycle control, and apoptosis. Consistently, Gadd45a has previously been shown to interact in vitro and/or in vivo with a number of proteins playing central roles in these cellular processes: proliferating cell nuclear antigen, p21(Cip1/Waf1), Cdc2-CyclinB complex, **MTK1**, and histones. Adding to this complexity, we have found that Gadd45a self-associates in solution, both in vitro and when expressed in the cell. Moreover, Gadd45a can complex with the two other members of the Gadd45 family of stress-induced proteins, human Gadd45b (MyD118) and Gadd45g (CR6). Gel-exclusion chromatography, native gel electrophoretic analysis, enzyme-linked immunosorbent assay, and chemical cross-linking showed that recombinant Gadd45a forms dimeric, trimeric, and tetrameric species in vitro, the dimers being the predominant form. Deletion mutant and peptide scanning analyses suggest that Gadd45a has two self-association sites: within N-terminal amino acids 33-61 and within 40 C-terminal amino acids. Despite the low abundance of Gadd45a in the cell, oligomer-forming concentrations can probably be achieved in the foci-like nuclear structures formed by the protein upon overexpression. Evidence for a potential role of Gadd45a self-association in altering DNA accessibility on damaged nucleosomes is presented.

L2 ANSWER 11 OF 51 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001528126 MEDLINE
DOCUMENT NUMBER: 21458432 PubMed ID: 11574474
TITLE: A Drosophila MAPKKK, D-MEKK1, mediates stress responses through activation of p38 MAPK.
AUTHOR: Inoue H; Tateno M; Fujimura-Kamada K; Takaesu G; Adachi-Yamada T; Ninomiya-Tsuji J; Irie K; Nishida Y; Matsumoto K
CORPORATE SOURCE: Department of Molecular Biology, Graduate School of Science, Nagoya University and CREST, Japan Science and

Technology Corporation, Chikusa-ku, Nagoya 464-8602, Japan.
SOURCE: EMBO JOURNAL, (2001 Oct 1) 20 (19) 5421-30.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB069961; GENBANK-AB069962
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20020420
Entered Medline: 20011204

AB In cultured mammalian cells, the p38 mitogen-activated protein kinase (MAPK) pathway is activated in response to a variety of environmental stresses. How ever, there is little evidence from in vivo studies to demonstrate a role for this pathway in the stress response. We identified a Drosophila MAPK kinase kinase (MAPKKK), D-MEKK1, which can activate p38 MAPK. D-MEKK1 is structurally similar to the mammalian **MEKK4/MTK1** MAPKKK. D-MEKK1 kinase activity was activated in animals under conditions of high osmolarity. Drosophila mutants lacking D-MEKK1 were hypersensitive to environmental stresses, including elevated temperature and increased osmolarity. In these D-MEKK1 mutants, activation of Drosophila p38 MAPK in response to stress was poor compared with activation in wild-type animals. These results suggest that D-MEKK1 regulation of the p38 MAPK pathway is critical for the response to environmental stresses in Drosophila.

L2 ANSWER 12 OF 51 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:525041 CAPLUS
DOCUMENT NUMBER: 135:255297
TITLE: Novel patterns of gene expression in pituitary adenomas identified by complementary deoxyribonucleic acid microarrays and quantitative reverse transcription-polymerase chain reaction
AUTHOR(S): Evans, Chheng-Orn; Young, Andrew N.; Brown, Milton R.; Brat, Daniel J.; Parks, John. S.; Neish, Andrew S.; Oyesiku, Nelson M.
CORPORATE SOURCE: Department of Neurosurgery and Laboratory of Molecular Neurosurgery and Biotechnology, Emory University School of Medicine, Atlanta, GA, 30322, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (2001), 86(7), 3097-3107
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pituitary adenomas account for approx. 10% of intracranial tumors, but little is known of the oncogenesis of these tumors. The identification of tumor-specific genes may further elucidate the pathways of tumor formation. We used complementary DNA microarrays to examine gene expression profiles in nonfunctioning, PRL, GH, and ACTH secreting adenomas, compared with normal pituitary. Microarray anal. showed that 128 of 7075 genes examd. were differentially expressed. We then analyzed three genes with unique expression patterns and oncogenic importance by RT-real time quant. PCR in 37 pituitaries. Folate receptor gene was significantly overexpressed in nonfunctioning adenomas but was significantly underexpressed in PRL and GH adenomas, compared with controls and to other tumors. The ornithine decarboxylase gene was significantly overexpressed in GH adenomas, compared with other tumor subtypes but was significantly underexpressed in ACTH adenomas. C-mer proto-oncogene tyrosine kinase gene was significantly overexpressed in

ACTH adenomas but was significantly underexpressed in PRL adenomas. We have shown that at least three genes involved in carcinogenesis in other tissues are also aberrantly regulated in the major types of pituitary tumors. The evaluation of candidate genes that emerge from these expts. provides a rational approach to investigate those genes significant in tumorigenesis.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 51 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001408766 EMBASE
TITLE: Specific amino acid deficiency alters the expression of genes in human melanoma and other tumor cell lines.
AUTHOR: Meadows G.G.; Zhang H.; Ge X.
CORPORATE SOURCE: G.G. Meadows, Can. Prevention/Research Center, College of Pharmacy, Washington State University, Pullman, WA 99164-6510, United States. meadows@wsu.edu
SOURCE: Journal of Nutrition, (2001) 131/11 SUPPL. (3047S-3050S). Refs: 25
ISSN: 0022-3166 CODEN: JONUAI
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This study determined the effect of tyrosine (Tyr) and phenylalanine (Phe) deprivation on protein expression and phosphorylation of **mitogen -activated protein kinase 4** (MKK4)/stress-activated protein/Erk kinase (SEK1), a metastasis suppressor gene. Differential display and suppressive subtractive hybridization techniques identified genes modulated by Tyr and Phe deprivation. Expression of MKK4/SEK1 protein varied widely among human A375, A375SM and SB2 melanoma, PC-3 and DU145 prostate cancer, and MDA-MB-231 breast cancer cell lines and within the different lines. Phosphorylation of the MKK4/SEK1 protein similarly varied. No differences in MKK4/SEK1 gene expression or in the 41 other metastasis and tumor suppressor genes were found in A375 melanoma cells cultured in Tyr- and Phe-deprived media. A number of up-regulated and down-regulated genes in A375 melanoma cells were identified by differential display and suppressive subtractive hybridization that were pertinent to regulation of cytoskeletal organization, cell movement, gene transcription and metastasis. Two tumor marker genes, the gene for enolase and FUS/CHOP, were down-regulated by Tyr and Phe deprivation. This study shows that tumor cells display heterogeneity in their response to deprivation of Tyr and Phe and that these amino acids may be signaling molecules that regulate gene expression and function in tumor cells.

L2 ANSWER 14 OF 51 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4

ACCESSION NUMBER: 2001:281970 CAPLUS
DOCUMENT NUMBER: 135:254960
TITLE: Ectopic expression of MyD118/Gadd45/CR6 (Gadd45.beta./.alpha./.gamma.) sensitizes neoplastic cells to genotoxic stress-induced apoptosis
AUTHOR(S): Zhang, Wei; Hoffman, Barbara; Liebermann, Dan A.
CORPORATE SOURCE: Fels Institute For Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, PA, 19140, USA

SOURCE: International Journal of Oncology (2001), 18(4), 749-757
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The MyD118/Gadd45/CR6 gene family (also termed Gadd45.beta./.alpha./.gamma.) has been identified as genes which are rapidly induced by genotoxic agents, during terminal differentiation, as well as by apoptotic cytokines. In recent years, evidence has emerged that the proteins encoded by these genes play pivotal roles in neg. growth control, including growth suppression and apoptotic cell death. However, under what physiol. condition these proteins mediate either cell cycle arrest or apoptosis, and the mol. nature of apoptotic pathways involved are currently unclear. Thus, to further explore the effects of these genes on cell growth and cell viability, either in the presence or absence of extrinsic stress, we have established M1 myeloblastic leukemia and H1299 lung carcinoma cell lines, where high level ectopic expression of MyD118, Gadd45, or CR6 can be induced by iso-Pr .beta.-D-thiogalactopyranoside (IPTG). By taking advantage of these cell lines, it was obsd. that in the absence of genotoxic stress, inducible expression of MyD118, Gadd45 and/or CR6 resulted in retardation of cellular proliferation and accumulation of cells in the G1 phase of the cell cycle. Ectopic expression of these proteins also was found to sensitize the cells to apoptosis induced by genotoxic agents such as UV, MMS, .gamma.-irradn. and VP16. Finally, evidence has been obtained that in the absence of stress, ectopic expression of MyD118/Gadd45/CR6 is insufficient to activate the **MTK1**/JNK/p38 stress cascade, and that enhancement of genotoxic stress induced apoptosis by these proteins may involve apoptotic pathways other than the JNK/p38 pathways.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 15 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:289454 BIOSIS
DOCUMENT NUMBER: PREV200100289454
TITLE: IL-18-stimulated GADD45beta required in cytokine-induced, but not TCR-induced, IFN-gamma production.
AUTHOR(S): Yang, Jianfei (1); Zhu, Hong (1); Murphy, Theresa L. (1); Ouyang, Wenjun (1); Murphy, Kenneth M. (1)
CORPORATE SOURCE: (1) Washington University School of Medicine, 660 S. Euclid, St. Louis, MO, 63108 USA
SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A713. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Two distinct physiologic stimuli can induce IFN-gamma production in Th1 cells. T cell receptor (TCR) signaling induces IFN-gamma transcription by a Cyclosporin A (CsA)-sensitive pathway. In contrast, certain cytokines, in particular IL-12 and IL-18, exert powerfully synergistic induction of IFN-gamma transcription that is TCR-independent, not inhibited by CsA, and

requires new protein synthesis. To characterize this TCR-independent cytokine-induced IFN-gamma pathway, we screened for genes selectively induced in IL-12/IL-18-treated Th1 cells. GADD45beta, which binds and activates **MEKK4**, was induced by IL-18 and augmented by IL-12 in Th1 cells. Expression of GADD45beta in naive CD4+ T cells activated p38 MAPK and increased cytokine-induced, but not TCR-induced, IFN-gamma production. A kinase-inactive **MEKK4** that can sequester GADD45betainhibits cytokine-induced, but not TCR-induced, IFN-gamma production. Finally, inhibition of p38 MAPK activity selectively blocked cytokine-induced, but not TCR-induced, IFN-gamma production. Thus, IL-12/IL-18-induced IFN-gamma transcription involves induction of GADD45beta and activation of **MEKK4**, and requires downstream p38 MAPK activation, whereas TCR-induced IFN-gamma production does not require this pathway of p38 MAPK activation.

L2 ANSWER 16 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:474499 BIOSIS
DOCUMENT NUMBER: PREV200100474499
TITLE: Expression and phosphorylation of mitigen-activated protein kinases in melanoma cells in vitro and in vivo. Evidence for a correlation between in vivo phosphorylation and tumor progression.
AUTHOR(S): Boehm, M. (1); Wolff, I. (1); Metze, D. (1); Luger, T. (1)
CORPORATE SOURCE: (1) Department of Dermatology and Ludwig Boltzmann Institute for Cell Biology and Immunobiology of the Skin, University of Muenster, Muenster Germany
SOURCE: Journal of Investigative Dermatology, (August, 2001) Vol. 117, No. 2, pp. 473. print.
Meeting Info.: 62nd Annual Meeting of the Society for Investigative Dermatology Washington, DC, USA May 09-12, 2001
ISSN: 0022-202X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L2 ANSWER 17 OF 51 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001175092 MEDLINE
DOCUMENT NUMBER: 21170150 PubMed ID: 11175814
TITLE: IL-18-stimulated GADD45 beta required in cytokine-induced, but not TCR-induced, IFN-gamma production.
COMMENT: Comment in: Nat Immunol. 2001 Feb;2(2):140-2
AUTHOR: Yang J; Zhu H; Murphy T L; Ouyang W; Murphy K M
CORPORATE SOURCE: Department of Pathology and Immunology, Howard Hughes Medical Institute, Washington University School of Medicine, 660 South Euclid Ave., St. Louis, MO 63110, USA.
SOURCE: Nat Immunol, (2001 Feb) 2 (2) 157-64.
Journal code: D0G; 100941354. ISSN: 1529-2908.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412
AB Interleukin-12 (IL-12) and IL-18 induce synergistic transcription of interferon gamma (IFN-gamma) that is T cell receptor (TCR)-independent, not inhibited by cyclosporin A and requires new protein synthesis. To characterize this pathway, we screened for genes that are induced in IL-12- and IL-18-treated T helper type 1 cells. GADD45 beta, which activates mitogen-activated protein kinase (MAPK)-extracellular

signal-regulated kinase kinase 4 (**MEKK4**), was induced by IL-18 and augmented by IL-12. GADD45 beta expression in naive CD4+ T cells activated p38 MAPK and selectively increased cytokine-induced, but not TCR-induced, IFN-gamma production. Kinase-inactive **MEKK4** and inhibition of the p38 MAPK pathway both selectively inhibit cytokine-induced, but not TCR-induced, IFN-gamma production. Thus, the synergy between IL-12 and IL-18 may involve GADD45 beta induction, which can maintain the **MEKK4** and p38 MAPK activation that is necessary for cytokine-induced, but not TCR-induced, IFN-gamma production.

L2 ANSWER 18 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:369662 BIOSIS
DOCUMENT NUMBER: PREV200100369662
TITLE: Expression of mitogen activated protein kinase kinase 4 (MKK4), a metastasis suppressor gene, is downregulated in ovarian carcinomas.
AUTHOR(S): Yamada, Seiko Diane (1); Montag, Anthony G. (1); Benson, David (1); Hrobowski, Yancey (1); Rinker-Schaeffer, Carrie (1)
CORPORATE SOURCE: (1) University of Chicago, Chicago, IL USA
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (March, 2001) Vol. 42, pp. 121. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L2 ANSWER 19 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:129769 BIOSIS
DOCUMENT NUMBER: PREV200200129769
TITLE: MyD118/GADD45/CR6 (GADD45b,g,a) modulate blood cell homeostatis & response to genotoxic stress.
AUTHOR(S): Liebermann, Dan A. (1); Amanullah, Arshad (1); Balliet, Arthur (1); Azam, Naiyer (1); Zhang, Wei (1); Hoffman, Barbara (1)
CORPORATE SOURCE: (1) Fels Inst. and Biochemistry, Temple University School of Medicine, Philadelphia, PA USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 79a-80a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The MyD118/GADD45/CR6 family of proteins (also termed GADD45b, Gadd45a and GADD45g), rapidly induced by genotoxic agents as well as by terminal differentiation and apoptotic cytokines, play pivotal roles in negative growth control, DNA repair and innate immunity. MyD118/GADD45/CR6 serve similar, but not identical, functions along different apoptotic and growth inhibitory pathways, and display a complex array of physical interactions, including homologous and heterologous interactions with each other, as well as with other cellular proteins (PCNA, p21, Cdc2, **MTK1**, core histones). Using mice deficient for either MyD118, GADD45a or CR6, or both GADD45a and MyD118, and myeloid differentiation inducible cell lines conditionally expressing GADD45 proteins, or antisense oligomers to block GADD45 expression, has provided evidence that GADD45 proteins play a role

in regulating homeostasis of hematopoietic tissues by modulating both the cell cycle and apoptosis in response to differentiation and growth inhibitory cytokines, such as TGFb, and in response to genotoxic stress. Thus alterations in expression of GADD45 proteins are expected to modify cell cycle controls and survival, and to manifest itself by changing the distribution of different lineages and stages of maturation of hematopoietic cells. Understanding how these proteins function to regulate blood cell homeostasis, and host responses to stress should contribute to a greater understanding of the genetic events involved in the pathogenesis of different leukemias and the response of normal and malignant hematopoietic cells to chemo- and radiation- therapy, ultimately aiding in diagnosis, prognosis and therapy.

L2 ANSWER 20 OF 51 USPATFULL

ACCESSION NUMBER:	2000:74127 USPATFULL
TITLE:	MEKK proteins
INVENTOR(S):	Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S):	National Jewish Center For Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6074861		20000613
APPLICATION INFO.:	US 1995-461145		19950605 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-440421, filed on 12 May 1995 which is a continuation-in-part of Ser. No. US 1995-354516, filed on 21 Feb 1995, now abandoned which is a division of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941, issued on 11 Apr 1995 And a continuation-in-part of Ser. No. US 1994-323460, filed on 14 Oct 1994, now patented, Pat. No. US 5854043 And a continuation-in-part of Ser. No. WO 1994-US11690, filed on 14 Oct 1994 And a continuation-in-part of Ser. No. WO 1994-US4178, filed on 15 Apr 1994 which is a continuation-in-part of Ser. No. US 49254

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Prouty, Rebecca E.
ASSISTANT EXAMINER:	Monshipouri, M.
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP, DeConti, Jr., Esq., Giulio A., Lauro, Esq., Peter C.
NUMBER OF CLAIMS:	24
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	44 Drawing Figure(s); 36 Drawing Page(s)
LINE COUNT:	4631

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to isolated MEKK proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods to use such proteins to regulate signal transduction in a cell. The present invention also includes therapeutic compositions comprising such proteins or nucleic acid molecules that encode such proteins and their use to treat animals having medical disorders including cancer, inflammation, neurological disorders, autoimmune diseases, allergic reactions, and hormone-related diseases. When MEKK is expressed, it phosphorylates and activates MEKs including MEK-1, MEK-2 and JEK.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 21 OF 51 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 2001038225 MEDLINE
DOCUMENT NUMBER: 20517905 PubMed ID: 10938285
TITLE: BRCA1 facilitates stress-induced apoptosis in breast and ovarian cancer cell lines.
AUTHOR: Thangaraju M; Kaufmann S H; Couch F J
CORPORATE SOURCE: Departments of Laboratory Medicine and Pathology, Oncology,
Molecular Pharmacology, and Biochemistry and Molecular Biology Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.
CONTRACT NUMBER: CA69008 (NCI)
CA78878 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 27) 275 (43) 33487-96.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001124

AB The BRCA1 tumor suppressor gene has previously been implicated in induction of high levels of apoptosis in osteocarcinoma cell lines. Overexpression of BRCA1 was shown to induce an apoptotic signaling pathway involving the c-Jun N-terminal kinase (JNK), but the signaling steps upstream and downstream of JNK were not delineated. To better understand the role of BRCA1 in apoptosis, we examined the effect of wild-type and C-terminal-truncated dominant negative BRCA1 on breast and ovarian cancer cell lines subjected to a number of different pro-apoptotic stimuli, including growth factor withdrawal, substratum detachment, ionizing radiation, and treatment with anticancer agents. All of these treatments were found to induce substantial levels of apoptosis in the presence of wild-type BRCA1, whereas dominant negative BRCA1 truncation mutants diminished the apoptotic response. Subsequent mapping of the apoptotic pathway induced by growth factor withdrawal demonstrated that BRCA1 enhanced signaling through a pathway that sequentially involved H-Ras, **MEKK4**, JNK, Fas ligand/Fas interactions, and caspase-9 activation. In addition, the pathway functioned independently of the p53 tumor suppressor. These data suggest that BRCA1 is an important modulator of the response to cellular stress and that loss of this apoptotic potential due to BRCA1 mutations may contribute to tumor development.

L2 ANSWER 22 OF 51 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:664942 CAPLUS
DOCUMENT NUMBER: 133:276785
TITLE: c-Jun inhibits transforming growth factor .beta.-mediated transcription by repressing Smad3 transcriptional activity
AUTHOR(S): Dennler, Sylviane; Prunier, Celine; Ferrand, Nathalie;
Gauthier, Jean-Michel; Atfi, Azeddine
CORPORATE SOURCE: Laboratoire GlaxoWellcome, Les Ulis, 91951, Fr.
SOURCE: Journal of Biological Chemistry (2000), 275(37), 28858-28865
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Transforming growth factor .beta. (TGF-.beta.) is a pleiotropic cytokine that exerts its effects through a heteromeric complex of transmembrane serine/threonine kinase receptors. At least two intracellular pathways

are activated by TGF-.beta. as follows: the SAPK/JNK, involving the MEKK1,
MKK4, and JNK cascade, and the Smad pathway. Here, the authors report that the SAPK/JNK pathway inhibits the Smad3 pathway. Expression of dominant neg. or constitutively active mutants of kinases of the SAPK/JNK pathway, resp., activates or represses a TGF-.beta.-induced reporter contg. Smad3-binding sites. This effect is not dependent on blocking of Smad3 nuclear translocation but involves a functional interaction between Smad3 and c-Jun, a transcription factor activated by the SAPK/JNK pathway.
Overexpression of constitutively active MEKK1 or MKK4 mutants stabilizes the phys. interaction between Smad3 and c-Jun, whereas dominant neg. mutants inhibit this interaction. Moreover, overexpression of wild-type c-Jun inhibits Smad3-dependent transcription. However, c-Jun does not inhibit Smad3 binding to DNA in vitro. The repression obtained with a c-Jun mutant unable to activate transcription through AP-1 sites indicates
that the inhibitory mechanism does not rely on the induction of a Smad3 repressor by c-Jun, suggesting that c-Jun could act as a Smad3 co-repressor. The inhibition of the Smad3 pathway by the SAPK/JNK pathway, both triggered by TGF-.beta., could participate in a neg. feed-back loop to control TGF-.beta. responses.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 23 OF 51 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000420889 MEDLINE
DOCUMENT NUMBER: 20379047 PubMed ID: 10807916
TITLE: **MEKK4** mediates differentiation in response to retinoic acid via activation of c-Jun N-terminal kinase in rat embryonal carcinoma P19 cells.
AUTHOR: Kanungo J; Potapova I; Malbon C C; Wang H y
CORPORATE SOURCE: Department of Molecular Pharmacology, University Medical Center, SUNY/Stony Brook, Stony Brook, New York 11794-8651,
USA.
CONTRACT NUMBER: DK30111 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Aug 4) 275 (31) 24032-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20020420
Entered Medline: 20000907
AB Differentiation of P19 embryonal carcinoma cells in response to the morphogen retinoic acid is regulated by Galpha(12/13) and is associated with activation of c-Jun N-terminal kinase. The role of MEKK1 and **MEKK4** upstream of the c-Jun N-terminal kinase was investigated in P19 cells. P19 clones stably expressing constitutively active and dominant
negative mutants of MEKK1 and **MEKK4** were created and characterized. Expression of the constitutively active form of either MEKK1 or **MEKK4** mimicked the action of retinoic acid, inducing these embryonal carcinoma cells to primitive endoderm. Expression of the dominant negative form of MEKK1 had no influence on the ability of retinoic acid to induce either JNK activation or primitive endoderm formation in P19 stem cells. Expression of the dominant negative form of **MEKK4**, in contrast, effectively blocks both morphogen-induced activation of JNK and cellular differentiation. These data identify **MEKK4** as upstream of c-Jun N-terminal kinase in the pathway

mediating differentiation of P19 stem cells to primitive endoderm.

L2 ANSWER 24 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:436650 BIOSIS
DOCUMENT NUMBER: PREV200000436650
TITLE: Homocysteine-responsive ATF3 gene expression in human vascular endothelial cells: Activation of c-Jun NH2-terminal kinase and promoter response element.
AUTHOR(S): Cal, Yong; Zhang, Chun; Nawa, Tigre; Aso, Teijiro; Tanaka, Makiko; Oshiro, Satoru; Ichijo, Hidenori; Kitajima, Shigetaka (1)
CORPORATE SOURCE: (1) Department of Biochemical Genetics, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo, 113-8510 Japan
SOURCE: Blood, (September 15, 2000) Vol. 96, No. 6, pp. 2140-2148. print.
ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Activating transcription factor (ATF) 3 is a member of ATF/cyclic adenosine monophosphate (cAMP)-responsive element binding protein (ATF/CREB) family of transcription factors and functions as a stress-inducible transcriptional repressor. To understand the stress-induced gene regulation by homocysteine, we investigated activation of the ATF3 gene in human endothelial cells. Homocysteine caused a rapid induction of ATF3 at the transcriptional level. This induction was preceded by a rapid and sustained activation of c-Jun NH2-terminal kinase/stress-activated protein kinase (JNK/SAPK), and dominant negative mitogen-activated protein kinase kinase 4 and 7 abolished these effects. The effect of homocysteine appeared to be specific, because cysteine or homocystine had no appreciable effect, but it was mimicked by dithiothreitol and beta-mercaptoethanol as well as tunicamycin. The homocysteine effect was not inhibited by an active oxygen scavenger. Deletion analysis of the 5' flanking sequence of the ATF3 gene promoter revealed that one of the major elements responsible for the induction by homocysteine is an ATF/cAMP responsive element (CRE) located at -92 to -85 relative to the transcriptional start site. Gel shift, immunoprecipitation, and cotransfection assays demonstrated that a complex (or complexes) containing ATF2, c-Jun, and ATF3 increased binding to the ATF/CRE site in the homocysteine-treated cells and activated the ATF3 gene expression, while ATF3 appeared to repress its own promoter. These data together suggested a novel pathway by which homocysteine causes the activation of JNK/SAPK and subsequent ATF3 expression through its reductive stress. Activation of JNK/SAPK and ATF3 expression in response to homocysteine may have a functional role in homocysteinemia-associated endothelial dysfunction.

L2 ANSWER 25 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:49456 BIOSIS
DOCUMENT NUMBER: PREV200100049456
TITLE: Arabidopsis MAP kinase 4 negatively regulates systemic acquired resistance.
AUTHOR(S): Petersen, Morten; Brodersen, Peter; Naested, Henrik; Andreasson, Erik; Lindhart, Ursula; Johansen, Bo; Nielsen, Henrik B.; Lacy, Michelle; Austin, Mark J.; Parker, Jane E.; Sharma, Sashi B.; Klessig, Daniel F.; Martienssen, Rob; Mattsson, Ole; Jensen, Anders B.; Mundy, John (1)
CORPORATE SOURCE: (1) Institute of Molecular Biology, Copenhagen University, Oster Farimagsgade 2A, 1353, Copenhagen K: mundy@biobase.dk

Denmark
SOURCE: Cell, (December 22, 2000) Vol. 103, No. 7, pp. 1111-1120. print.
ISSN: 0092-8674.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Transposon inactivation of Arabidopsis MAP kinase 4 produced the mpk4 mutant exhibiting constitutive systemic acquired resistance (SAR) including elevated salicylic acid (SA) levels, increased resistance to virulent pathogens, and constitutive pathogenesis-related gene expression shown by Northern and microarray hybridizations. MPK4 kinase activity is required to repress SAR, as an inactive MPK4 form failed to complement mpk4. Analysis of mpk4 expressing the SA hydroxylase NahG and of mpk4/npr1 double mutants indicated that SAR expression in mpk4 is dependent upon elevated SA levels but is independent of NPR1. PDF1.2 and THI2.1 gene induction by jasmonate was blocked in mpk4 expressing NahG, suggesting that MPK4 is required for jasmonic acid-responsive gene expression.

L2 ANSWER 26 OF 51 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000441833 MEDLINE
DOCUMENT NUMBER: 20384190 PubMed ID: 10924369
TITLE: Cloning of DPK, a novel dendritic cell-derived protein kinase activating the ERK1/ERK2 and JNK/SAPK pathways.
AUTHOR: Zhang W; Chen T; Wan T; He L; Li N; Yuan Z; Cao X
CORPORATE SOURCE: Department of Immunology, Second Military Medical University, 800 Xiangyin Road, Shanghai, 200433, People's Republic of China.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Aug 11) 274 (3) 872-9.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000915
AB Mitogen-activated protein kinase (MAPK) cascades are the major signaling systems transducing extracellular signals into intracellular responses, which mainly include the extracellular signal-regulated kinase (ERK) pathway, the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) pathway, and the p38 pathway. From dendritic cell cDNA library, we isolated a full-length cDNA encoding a potentially novel 898-residue kinase, which was designated DPK. The protein contained a potential kinase domain at the N-terminal exhibiting homology with MEKK1-, MEKK2-, MEKK3-, **MEKK4**-, MEKK5-, Tpl-2-, and p21-activated kinases (PAKs), but no GTPase-binding domain which is characteristic of PAKs. Northern blotting analysis showed that DPK was ubiquitously expressed in normal tissues, with abundant expression in kidney, skeletal muscle, heart, and liver. When overexpressed in transfected NIH3T3 cells, it could activate both the ERK1/ERK2 pathway and the SAPK pathway in a dose-dependent manner, but not affect the p38 pathway. These findings suggested that DPK might be a novel candidate MAPKKK.

L2 ANSWER 27 OF 51 BIOSIS
ACCESSION NUMBER: 2001:102246 BIOSIS
DOCUMENT NUMBER: PREV200100102246

TITLE: Various abiotic stresses rapidly activate Arabidopsis MAP kinases ATMPK4 and ATMPK6.
AUTHOR(S): Ichimura, Kazuya; Mizoguchi, Tsuyoshi; Yoshida, Riichiro; Yuasa, Takashi; Shinozaki, Kazuo (1)
CORPORATE SOURCE: (1) Laboratory of Plant Molecular Biology, RIKEN Tsukuba Institute, 3-1-1 Koyadai, Tsukuba, Ibaraki, 305-0074: sinozaki@rtc.riken.go.jp Japan
SOURCE: Plant Journal, (December, 2000) Vol. 24, No. 5, pp. 655-665. print.
ISSN: 0960-7412.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Mitogen-activated protein kinase (MAP kinase, MAPK) cascades play pivotal roles in signal transduction of extracellular stimuli, such as environmental stresses and growth regulators, in various organisms. Arabidopsis thaliana MAP kinases constitute a gene family, but stimulatory signals for each MAP kinase have not been elucidated. Here we show that environmental stresses such as low temperature, low humidity, hyper-osmolarity, touch and wounding induce rapid and transient activation of the Arabidopsis MAP kinases ATMPK4 and ATMPK6. Activation of ATMPK4 and ATMPK6 was associated with tyrosine phosphorylation but not with the amounts of mRNA or protein. Kinetics during activation differ between these two MAP kinases. These results suggest that ATMPK4 and ATMPK6 are involved in distinct signal transduction pathways responding to these environmental stresses.

L2 ANSWER 28 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:26352 BIOSIS
DOCUMENT NUMBER: PREV200100026352
TITLE: The ras radioresistance signal transduction pathway.
AUTHOR(S): Gupta, A. K. (1); Bakanauskas, V. J. (1); Bernhard, E. J. (1); Muschel, R. J. (1); McKenna, W. G. (1)
CORPORATE SOURCE: (1) University of Pennsylvania, Philadelphia, PA USA
SOURCE: International Journal of Radiation Oncology Biology Physics, (2000) Vol. 48, No. 3 Supplement, pp. 245-246. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Therapeutic Radiology and Oncology Boston, Massachusets, USA October 22-26, 2000 American Society for Therapeutic Radiology and Oncology
. ISSN: 0360-3016.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L2 ANSWER 29 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:289134 BIOSIS
DOCUMENT NUMBER: PREV200100289134
TITLE: MyD118/GADD45/CR6 (GADD45beta,alpha,gamma) in blood cell homeostasis.
AUTHOR(S): Liebermann, Dan A.; Zhang, Wei; Balliet, Arthur; Azam, Naiyer; Vairapandi, Mariappan; Hoffman, Barbara
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 146b. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The MyD118/Gadd45/CR6 family of proteins (also termed

GADD45beta,alpha,gamma) are rapidly induced by genotoxic agents, as well as by terminal differentiation and apoptotic cytokines, and the proteins encoded by these genes play pivotal roles in negative growth control. MyD118/GADD45/CR6 serve similar, but not identical, functions along different apoptotic and growth inhibitory pathways, and display a complex array of physical interactions, including homologous and heterologous interactions with each other, as well as with other cellular proteins (PCNA, p21, Cdc2, **MTK1**, core histones). The combined use of M1 myeloblastic leukemia cells which ectopically express inducible GADD45 proteins, antisense oligomers to block their expression, and mice deficient for GADD45 has provided evidence that MyD118/Gadd45/CR6 play a role in regulating homeostasis of hematopoietic tissues by modulating both the cell cycle and apoptosis in response to differentiation and growth inhibitory cytokines, and in response to genotoxic stress. Thus alterations in expression of MyD118/Gadd45/CR6 are expected to modify cell cycle controls and survival, and to manifest itself by changing the distribution of different lineages and stages of maturation of hematopoietic cells. Understanding how these proteins function to regulate blood cell homeostasis should contribute to a greater understanding of the genetic events involved in the pathogenesis of different leukemias and the response of normal and malignant hematopoietic cells to chemo- and radiation- therapy, ultimately aiding in diagnosis, prognosis and therapy.

L2 ANSWER 30 OF 51 LIFESCI COPYRIGHT 2002 CSA
ACCESSION NUMBER: 2000:98702 LIFESCI
TITLE: Assignment of human GADD45G to chromosome 9q22.1 arrow right q22.3 by radiation hybrid mapping
AUTHOR: Gong, R.; Yu, L.; Zhang, H.; Tu, Q.; Zhao, Y.; Yang, J.; Xu, Y.; Zhao, S.
CORPORATE SOURCE: Institute of Genetics, Fudan University, 220 Handan Road, Shanghai 200433 P.R., China; E-mail: longyu@fudan.edu.cn
SOURCE: Cytogenetics and Cell Genetics [Cytogenet. Cell Genet.], (20000000) vol. 88, no. 1-2, pp. 95-96.
ISSN: 0301-0171.
DOCUMENT TYPE: Journal
FILE SEGMENT: G
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The growth arrest and DNA damage inducible (GADD) genes represent a family of genes that were identified on the basis of rapid induction by treatment with DNA-damaging agents or by certain growth arrest conditions (Fornace et al., 1988). GADD45, in particular, is a group of genes that are induced by a certain subset of environmental stresses, such as methyl methanesulfonate (MMS), ultraviolet, and ionizing radiation (Fornace et al., 1992). It has been reported that GADD45 played a role in negative growth control, including cell cycle arrest, DNA repair, and/or apoptosis (Liebermann et al., 1998). Recently, two cDNA sequences, which are 1378 bp and 1060 bp, respectively were isolated in our laboratory (GenBank) Accession No. AF087853 and AF087883). The cDNA nucleotide sequences predict two proteins of 160 amino acids and 159 amino acids, which were recently reported as GADD45 beta and GADD45 gamma (Takekawa et al., 1998).
Northern blot analysis of mRNA from human multiple tissues (MTN I and II, Clontech) detects predominant mRNA species about 1.4 kb for GADD45 beta and 1.35 kb for GADD45 gamma . The GADD45 beta is expressed in most tissues, with the exception of thymus, small intestine, and brain, whereas

the expression of GADD45 gamma was most abundant in the heart, placenta, skeletal muscle, prostate, testis, and ovary. Recent evidence suggested these GADD45-like proteins were able to activate **MTK1** (a human kinase MAPKKK) kinase activity, both in vivo and in vitro, via binding to an N-terminal domain of **MTK1**, which is upstream of both the p38 and JNK (c-Jun N-terminal kinase) MAPK pathway involved in apoptosis (Chen et al., 1996).

L2 ANSWER 31 OF 51 USPATFULL

ACCESSION NUMBER:	1999:141672 USPATFULL
TITLE:	Methods for regulating MEKK protein activity
INVENTOR(S):	Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S):	National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5981265		19991109
APPLICATION INFO.:	US 1995-461146		19950605 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-440421, filed on 12 May 1995 which is a continuation-in-part of Ser. No. US 1994-345516, filed on 28 Nov 1994, now abandoned which is a division of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941 And a continuation-in-part of Ser. No. US 1994-323460, filed on 14 Oct 1994 And a continuation-in-part of Ser. No. WO 1994-US11690, filed on 14 Oct 1994, now patented, Pat. No. WO 5854043 And a continuation-in-part of Ser. No. WO 1994-US4178, filed on 15 Apr 1994 which is a continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Spector, Lorraine
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Lauro, Peter C.
NUMBER OF CLAIMS:	3
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	40 Drawing Figure(s); 36 Drawing Page(s)
LINE COUNT:	5111

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to isolated MEKK proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods to use such proteins to regulate signal transduction in a cell. The present invention also includes therapeutic compositions comprising such proteins or nucleic acid molecules that encode such proteins and their use to treat animals having medical disorders including cancer, inflammation, neurological disorders, autoimmune diseases, allergic reactions, and hormone-related diseases. When MEKK is expressed, it phosphorylates and activates MEKs including MEK-1, MEK-2 and JEK.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 32 OF 51 USPATFULL

ACCESSION NUMBER:	1999:65175 USPATFULL
TITLE:	Regulation of cytokine production in a hematopoietic cell
INVENTOR(S):	Gelfand, Erwin W., Englewood, CO, United States Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S):	National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 5910417	19990608
APPLICATION INFO.:	US 1996-656563	19960531 (8)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Ulm, John	
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Lauro, Peter C.	
NUMBER OF CLAIMS:	2	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	28 Drawing Figure(s); 14 Drawing Page(s)	
LINE COUNT:	1661	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method useful for regulating cytokine production by a hematopoietic cell by regulating an MEKK/JNKK-contingent signal transduction pathway in such a cell is disclosed. Methods of identifying compounds capable of specifically regulating an MEKK/JNKK-contingent signal transduction pathway in hematopoietic cells, a kit for identifying cytokine regulators, methods to treat diseases involving cytokine production, and cells useful in such methods are also set forth.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 33 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER:	2000:75081 BIOSIS
DOCUMENT NUMBER:	PREV200000075081
TITLE:	COP9 signalosome-directed c-Jun activation/stabilization is independent of JNK.
AUTHOR(S):	Naumann, Michael (1); Bech-Otschir, Dawadschargal; Huang, Xiaohua; Ferrell, Katherine; Dubiel, Wolfgang
CORPORATE SOURCE:	(1) Abteilung Molekulare Biologie, Max-Planck-Institut fuer Infektionsbiologie, Humboldt University, 10117, Berlin Germany
SOURCE:	Journal of Biological Chemistry, (Dec. 10, 1999) Vol. 274, No. 50, pp. 35297-35300. ISSN: 0021-9258.
DOCUMENT TYPE:	Article
LANGUAGE:	English
SUMMARY LANGUAGE:	English

AB The basic region-leucine zipper transcription factor c-Jun regulates gene expression and cell function. It participates in the formation of homo- or heterodimeric complexes that specifically bind to DNA sequences called activating protein 1 (AP-1) sites. The stability and activity of c-Jun is regulated by phosphorylation within the N-terminal activation domain. Mitogen- and stress-activated c-Jun N-terminal kinases (JNKs) were previously the only described enzymes phosphorylating c-Jun at the N terminus in vivo. In this report we demonstrate a JNK-independent activation of c-Jun in vivo directed by the constitutive photomorphogenesis (COP9) signalosome. The overexpression of signalosome subunit 2 (Sgn2), a subunit of the COP9 signalosome, leads to de novo assembly of the complex with a partial incorporation of the overexpressed subunit. The de novo formation of COP9 signalosome parallels an increase of c-Jun protein resulting in elevated AP-1 transcriptional activity. The c-Jun activation caused by Sgn2 overexpression is independent of JNK and mitogen-activated protein kinase kinase 4. The data demonstrate the existence of a novel COP9 signalosome-directed c-Jun activation pathway.

L2 ANSWER 34 OF 51 MEDLINE DUPLICATE 9

ACCESSION NUMBER:	1999445500 MEDLINE
DOCUMENT NUMBER:	99445500 PubMed ID: 10514426
TITLE:	gadd45 is not required for activation of c-Jun N-terminal

kinase or p38 during acute stress.
AUTHOR: Wang X; Gorospe M; Holbrook N J
CORPORATE SOURCE: Laboratory of Biological Chemistry, NIA, National Institutes of Health, Baltimore, Maryland 21224, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Oct 15) 274 (42) 29599-602.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991119

AB Cells respond to environmental stress with activation of c-Jun N-terminal kinase (JNK) and p38. Recent studies have implicated Gadd45 and two related proteins, MyD118/Gadd45beta and CR6/Gadd45gamma, as initiators of JNK/p38 signaling via their interaction with an upstream kinase **MTK1**. It was proposed that stress-induced expression of the Gadd45-related proteins leads to **MTK1** activation and subsequent JNK/p38 activation. Using embryo fibroblasts from gadd45-null mice, we have addressed the requirement for Gadd45 in mediating JNK/p38 activation during acute stress. Comparison of JNK/p38 activities in response to methyl methanesulfonate, hydrogen peroxide, UVC irradiation, sorbitol, and anisomycin treatment of gadd45(+/+) and gadd45(-/-) fibroblasts revealed no deficiency in JNK/p38 activation in gadd45(-/-) fibroblasts. In addition, in wild type cells, JNK and p38 activation significantly preceded gadd45 induction with all stresses. Examination of myd118/gadd45beta and cr6/gadd45gamma expression in gadd45(+/+) and gadd45(-/-) fibroblasts revealed similar induction patterns in the two cell types, which, like gadd45 expression, was delayed relative to JNK/p38 activation. We conclude that gadd45 expression is not required for activation of JNK/p38 by environmental stresses, nor are stress-induced increases in myd118/gadd45beta and cr6/gadd45gamma expression necessary for kinase activation in response to such insults.

L2 ANSWER 35 OF 51 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999185046 MEDLINE
DOCUMENT NUMBER: 99185046 PubMed ID: 10085062
TITLE: Mitogen-activated protein kinase/ERK kinase kinases 2 and 3 activate nuclear factor-kappaB through IkappaB kinase-alpha and IkappaB kinase-beta.
AUTHOR: Zhao Q; Lee F S
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Mar 26) 274 (13) 8355-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 20020420
Entered Medline: 19990429

AB Recent evidence indicates that nuclear factor-kappaB (NF-kappaB), a transcription factor critically important for immune and inflammatory responses, is activated by a protein kinase cascade. The essential

features of this cascade are that a mitogen-activated protein kinase kinase kinase (MAP3K) activates an IkappaB kinase (IKK) that site-specifically phosphorylates IkappaB. The IkappaB protein, which ordinarily sequesters NF-kappaB in the cytoplasm, is subsequently degraded by the ubiquitin-proteasome pathway, thereby allowing the nuclear translocation of NF-kappaB. Thus far, only two MAP3Ks, NIK and MEKK1, have been identified that can activate this pathway. We now show that MEKK2 and MEKK3 can in vivo activate IKK-alpha and IKK-beta, induce site-specific IkappaBalpha phosphorylation, and, relatively modestly, activate an NF-kappaB reporter gene. In addition, dominant negative versions of either IKK-alpha or IKK-beta abolish NF-kappaB activation induced by MEKK2 or MEKK3, thereby providing evidence that these IKKs mediate the NF-kappaB-inducing activities of these MEKKs. In contrast, other MAP3Ks, including **MEKK4**, ASK1, and MLK3, fail to show evidence of activation of the NF-kappaB pathway. We conclude that a distinct subset of MAP3Ks can activate NF-kappaB.

L2 ANSWER 36 OF 51 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2000087182 MEDLINE
DOCUMENT NUMBER: 20087182 PubMed ID: 10618720
TITLE: Signal transduction pathways regulated by arsenate and arsenite.
AUTHOR: Porter A C; Fanger G R; Vaillancourt R R
CORPORATE SOURCE: Department of Pharmacology, College of Pharmacy, The University of Arizona, Tucson, Arizona, AZ 85721-0207, USA.
CONTRACT NUMBER: ES 06694 (NIEHS)
SOURCE: ONCOGENE, (1999 Dec 16) 18 (54) 7794-802.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000204

AB Arsenate and arsenite activate c-Jun N-terminal kinase (JNK), however, the mechanism by which this occurs is not known. By expressing inhibitory mutant small GTP-binding proteins, p21-activated kinase (PAK) and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase kinases (MEKKs), we have identified specific proteins that are involved in arsenate- and arsenite-mediated activation of JNK. We observe a distinct difference between arsenate and arsenite signaling, which demonstrates that arsenate and arsenite are capable of activating unique proteins. Both arsenate and arsenite activation of JNK requires Rac and Rho. Neither arsenate nor arsenite signaling was inhibited by a dominant-negative mutant of Cdc42 or Ras. Arsenite stimulation of JNK requires PAK, whereas arsenate-mediated activation of JNK was unaffected by inhibitory mutant PAK. Of the four MEKKs tested, only MEKK3 and **MEKK4** are involved in arsenate-mediated activation of JNK. In contrast, arsenite-mediated JNK activation requires MEKK2, MEKK3 and **MEKK4**. These results better define the mechanisms by which arsenate and arsenite activate JNK and demonstrate differences in the regulation of signal transduction pathways by these inorganic arsenic species.

L2 ANSWER 37 OF 51 LIFESCI COPYRIGHT 2002 CSA
ACCESSION NUMBER: 2000:36387 LIFESCI
TITLE: Concentration-dependent positive and negative regulation of

a MAP kinase by a MAP kinase kinase
AUTHOR: Kieran, M.W.; Katz, S.; Vail, B.; Zon, L.I.; Mayer, B.J.*
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, Harvard Medical School, Howard Hughes Medical Institute, Children's Hospital, 320 Longwood Avenue, Boston, Massachusetts, MA 02115, USA
SOURCE: Oncogene, (19991118) vol. 18, no. 48, pp. 6647-6657. ISSN: 0950-9232.
DOCUMENT TYPE: Journal
FILE SEGMENT: B
LANGUAGE: English
SUMMARY LANGUAGE: English

AB There are at least three distinct MAP kinase signaling modules in mammalian cells, distinguished by the family of kinases (Erk, SAPK/JNK, or p38) that is ultimately activated. Many input signals activate multiple MAP kinase cascades, and the mechanisms that control the specificity of signal output are not well understood. We show that SEK1/MKK4, a MAP kinase kinase proposed to activate SAPK/JNK, is a very potent inhibitor of p54 SAPK beta /JNK3 both in vitro and in vivo if present at equimolar or higher ratios. In contrast SEK can activate SAPK when present in substoichiometric amounts, but this activation is slow, consistent with the rate-limiting step in activation being the dissociation of an inactive SEK:SAPK complex. The N-terminal unique region of SEK is both necessary and partially sufficient for inhibition of SAPK, and is also necessary for activation of SAPK by SEK in vitro. We have also used the p38 MAP kinase and its activator MKK6 to examine the regulatory relationships among different kinases involved in stress responses. We show using purified kinases that inhibitory activity is specific for the combination of SEK and SAPK: SEK can activate but not inhibit p38, and MKK6 can activate but not inhibit SAPK beta and p38. These results reveal a potential mechanism for regulating stress-activated kinases, adding to a growing body of evidence suggesting that MAP kinases are controlled by relatively stable interactions with their activators.

L2 ANSWER 38 OF 51 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 12
ACCESSION NUMBER: 1999:419444 CAPLUS
DOCUMENT NUMBER: 131:210456
TITLE: Regulation of the human stress-responsive MAP kinase signaling pathways
AUTHOR(S): Saito, Haruo; Takekawa, Mutsuhiro
CORPORATE SOURCE: Div. Tumor Immunol., Dana-Farber Cancer Inst., Boston, 02115, USA
SOURCE: Seibutsu Butsuri Kagaku (1999), 43(2), 49-55
CODEN: SBBKA4; ISSN: 0031-9082
PUBLISHER: Nippon Denki Eido Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 7 refs. The MAP kinase signaling cascade (MAPKKK-MAPKK-MAPK) is well conserved in all eukaryotic cells. The yeast Hog cascade (Ssk2/Ssk22-Pbs2-Hog1) is structurally and functionally homologous to the mammalian stress-responsive p38 and JNK pathways that regulate apoptotic cell death. In order to identify pos. or neg. regulators for the p38 and JNK pathways, we devised several cloning strategies using the yeast HOG pathway mutants. First, we screened for human proteins whose expression in yeast complement the osmosensitivity of ssk2/ssk22.DELTA. mutations. Thus, we found a human homolog of yeast Ssk2/22 MAPKKKS, termed **MTK1**, which mediates the stress-induced activation of the p38 and JNK pathways in mammalian cells. Second, we identified three distinct GADD45-related proteins that bound to an

N-terminal domain of **MTK1** using a yeast two-hybrid method. The GADD45-related genes are induced by environmental stresses. Moreover, these proteins activated **MTK1** kinase activity both in vivo and in vitro, resulting in induction of p38/JNK activation and apoptosis which can be partially suppressed by coexpression of a dominant inhibitory **MTK1** mutant protein. These results indicate that the GADD45-related proteins mediate activation of the p38 and JNK pathways, via **MTK1**, in response to environmental stresses. Third, we screened for human cDNA clones that down-regulate the mutational hyperactivation of the yeast HOG pathway. The human PP2C.alpha. was found to neg. regulate the HOG pathway. Expression of PP2C.alpha. in mammalian cells inhibited activation of the p38 and JNK cascades but not the ERK pathway. These findings indicate that PP2C.alpha. plays a role in neg. regulation of mammalian stress responses.

L2 ANSWER 39 OF 51 USPATFULL

ACCESSION NUMBER:	1998:162314 USPATFULL
TITLE:	MEKK-related signal transduction kinases
INVENTOR(S):	Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S):	National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5854043		19981229
APPLICATION INFO.:	US 1994-323460		19941014 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Teng, Sally P.		
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Kara, Catherine J.		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	66 Drawing Figure(s); 32 Drawing Page(s)		
LINE COUNT:	3248		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to isolated MEKK proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods to use such proteins to regulate signal transduction in a cell. The present invention also includes therapeutic compositions comprising such proteins or nucleic acid molecules that encode such proteins and their use to treat animals having medical disorders including cancer, inflammation, neurological disorders, autoimmune diseases, allergic reactions, and hormone-related diseases. When MEKK is expressed, it phosphorylates and activates MEKs including MEK-1, MEK-2 and JEK.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 40 OF 51 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER:	1998:226389 BIOSIS
DOCUMENT NUMBER:	PREV199800226389
TITLE:	Human mitogen-activated protein kinase kinase 7 (MKK7) is a highly conserved c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) activated by environmental stresses and physiological stimuli.
AUTHOR(S):	Foltz, Ian N.; Gerl, Robert E.; Wieler, James S.; Luckach, Michael; Salmon, Ruth A.; Schrader, John W. (1)
CORPORATE SOURCE:	(1) Biomed. Res. Cent., Univ. B.C., Vancouver, BC V6T 1Z3 Canada

SOURCE: Journal of Biological Chemistry, (April 10, 1998) Vol. 273,
No. 15, pp. 9344-9351.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We report the cloning of a novel human activator of c-Jun N-terminal kinase (JNK), mitogen-activated protein kinase kinase 7 (MRK7). The mRNA for MKK7 is widely expressed in humans and mice and encodes a 47-kDa protein (419 amino acids), as determined by immunoblotting endogenous MKK7 with an antibody raised against its N terminus. The kinase domain of MKK7 is closely related to a Drosophila JNK kinase dHep (69% identity) and to a newly identified ortholog from Caenorhabditis elegans (54% identity), and was more distantly related to MKK4, MKK3, and MKK6. MKK7 phosphorylated and activated JNK1 but failed to activate p38 MAPK in co-expression studies. In hematopoietic cells, endogenous MKK7 was activated by treatment with the growth factor interleukin-3 (but not interleukin-4), or by ligation of CD40, the B-cell antigen receptor, or the receptor for the Fc fragment of immunoglobulin. MKK7 was also activated when cells were exposed to heat, UV irradiation, anisomycin, hyperosmolarity or the pro-inflammatory cytokine tumor necrosis factor-alpha. Co-expression of constitutively active mutants of RAS, RAC, or CDC42 in HeLa epithelial cells or of RAC or CDC42 in Ba/F3 factor-dependent hematopoietic cells also activated MKK7, suggesting that MKK7 will be involved in many physiological pathways.

L2 ANSWER 41 OF 51 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 1998123122 MEDLINE
DOCUMENT NUMBER: 98123122 PubMed ID: 9452471
TITLE: 14-3-3 proteins interact with specific MEK kinases.
AUTHOR: Fanger G R; Widmann C; Porter A C; Sather S; Johnson G L; Vaillancourt R R
CORPORATE SOURCE: Program in Molecular Signal Transduction, Division of Basic Sciences, National Jewish Medical and Research Center, Denver, Colorado 80206, USA.
CONTRACT NUMBER: DK37871 (NIDDK)
DK48845 (NIDDK)
GM18643-01 (NIGMS)
+
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Feb 6) 273 (6) 3476-83.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 20020420
Entered Medline: 19980305
AB MEK (mitogen-activated protein kinase/extracellular signal-regulated kinase kinase) kinases (MEKKs) regulate c-Jun N-terminal kinase and extracellular response kinase pathways. The 14-3-3zeta and 14-3-3epsilon isoforms were isolated in a two-hybrid screen for proteins interacting with the N-terminal regulatory domain of MEKK3. 14-3-3 proteins bound both the N-terminal regulatory and C-terminal kinase domains of MEKK3. The binding affinity of 14-3-3 for the MEKK3 N terminus was 90 nM, demonstrating a high affinity interaction. 14-3-3 proteins also interacted with MEKK1 and MEKK2, but not **MEKK4**. Endogenous 14-3-3 protein and MEKK1 and MEKK2 were similarly distributed in the cell, consistent

with their in vitro interactions. MEKK1 and 14-3-3 proteins colocalized using two-color digital confocal immunofluorescence. Binding of 14-3-3 proteins mapped to the N-terminal 393 residues of 196-kDa MEKK1. Unlike MEKK2 and MEKK3, the C-terminal kinase domain of MEKK1 demonstrated little or no ability to interact with 14-3-3 proteins. MEKK1, but not MEKK2, -3 or -4, is a caspase-3 substrate that when cleaved releases the kinase domain from the N-terminal regulatory domain. Functionally, caspase-3 cleavage of MEKK1 releases the kinase domain from the N-terminal 14-3-3-binding region, demonstrating that caspases can selectively alter protein kinase interactions with regulatory proteins. With regard to MEKK1, -2 and -3, 14-3-3 proteins do not appear to directly influence activity, but rather function as "scaffolds" for protein-protein interactions.

L2 ANSWER 42 OF 51 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 1999059689 MEDLINE
DOCUMENT NUMBER: 99059689 PubMed ID: 9841871
TITLE: Human mitogen-activated protein kinase kinase kinase mediates the stress-induced activation of mitogen-activated protein kinase cascades.
AUTHOR: Chan-Hui P Y; Weaver R
CORPORATE SOURCE: Amgen, Department of Inflammation Research, 3200 Walnut Street, Boulder, CO 80301, USA.. povying@stratabio.com
SOURCE: BIOCHEMICAL JOURNAL, (1998 Dec 15) 336 (Pt 3) 599-609. Journal code: 9YO; 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 20000303
Entered Medline: 19990225

AB The mitogen-activated protein kinase (MAPK) cascades represent one of the important signalling mechanisms in response to environmental stimuli. We report the identification of a human MAPK kinase kinase kinase, **MAPKKK4**, via sequence similarity with other MAPKKKs. When truncated **MAPKKK4** (DeltaMAPKKK4) was overexpressed in HEK293 cells, it was constitutively active and induced the activation of endogenous p38alpha, c-Jun N-terminal kinase (JNK)1/2 and extracellular signal-regulated kinase (ERK)2 in vivo. Kinase-inactive DeltaMAPKKK4 partly inhibited the activation of p38alpha, JNK1/2 and ERK2 induced by stress, tumour necrosis factor alpha or epidermal growth factor, suggesting that **MAPKKK4** might be physiologically involved in all three MAPK cascades. Co-expressed MAP kinase kinase (MKK)-1, MKK-4, MKK-3 and MKK-6 were activated in vivo by DeltaMAPKKK4. All of the above MKKs purified from Escherichia coli were phosphorylated and activated by DeltaMAPKKK4 immunoprecipitates in vitro. When expressed by lower plasmid doses, DeltaMAPKKK4 preferentially activated MKK-3 and p38alpha in vivo. Overexpression of DeltaMAPKKK4 did not activate the NF-kappaB pathway. Immunoprecipitation of endogenous **MAPKKK4** by specific antibodies showed that **MAPKKK4** was activated after the treatment of K562 cells with various stress conditions. As a broadly distributed kinase, **MAPKKK4** might serve as a stress responder. **MAPKKK4** is 91% identical with the recently described murine MEKK-4beta and might be its human homologue. It is also identical with the recently cloned human MAP three kinase 1 except for the lack of an internal sequence homologous to the murine MEKK-4alpha isoform. Differences in the reported functional activities of the three kinases are discussed.

L2 ANSWER 43 OF 51 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 1999043506 MEDLINE
DOCUMENT NUMBER: 99043506 PubMed ID: 9827804
TITLE: A family of stress-inducible GADD45-like proteins mediate activation of the stress-responsive **MTK1**/ **MEKK4** MAPKKK.
AUTHOR: Takekawa M; Saito H
CORPORATE SOURCE: Dana-Farber Cancer Institute, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: GM50909 (NIGMS)
GM56699 (NIGMS)
SOURCE: CELL, (1998 Nov 13) 95 (4) 521-30.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF078077; GENBANK-AF078078
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981215

AB The stress-responsive p38 and JNK MAPK pathways regulate cell cycle and apoptosis. A human MAPKKK, **MTK1** (= **MEKK4**), mediates activation of both p38 and JNK in response to environmental stresses. Using a yeast two-hybrid method, three related proteins, GADD45alpha (= GADD45), GADD45, (= MyD118), and GADD45gamma, were identified that bound to an N-terminal domain of **MTK1**. These proteins activated **MTK1** kinase activity, both in vivo and in vitro. The GADD45-like genes are induced by environmental stresses, including MMS, UV, and gamma irradiation. Expression of the GADD45-like genes induces p38/JNK activation and apoptosis, which can be partially suppressed by coexpression of a dominant inhibitory **MTK1** mutant protein. We propose that the GADD45-like proteins mediate activation of the p38/JNK pathway, via **MTK1**/ **MEKK4**, in response to environmental stresses.

L2 ANSWER 44 OF 51 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97166136 EMBASE
DOCUMENT NUMBER: 1997166136
TITLE: Characterization of the mitogen-activated protein kinase kinase 4 (MKKK4)/c-Jun NH2-terminal kinase 1 and MKK3/p38 pathways regulated by MEK kinases 2 and 3: MEK kinase 3 activates MKK3 but does not cause activation of p38 kinase In vivo.
AUTHOR: Deacon K.; Blank J.L.
CORPORATE SOURCE: J.L. Blank, Dept. of Cell Physiology/Pharmacogy, Medical Sciences Building, Univ. of Leicester School of Med., University Road, Leicester LE1 9HN, United Kingdom
SOURCE: Journal of Biological Chemistry, (1997) 272/22 (14489-14496).
Refs: 79
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We previously reported the isolation of cDNAs encoding two mammalian mitogen-activated protein kinase (MAPK)/extracellular-regulated kinase (ERK) kinase kinases, designated MEKK2 and MEKK3 (Blank, J. L., Gerwins, P., Elliott, E. M., Sather, S. and Johnson, G. L. (1996) J. Biol. Chem. 271, 5361-5368). In the present study, cotransfection experiments were used to examine the regulation by MEKK2 and MEKK3 of the dual specificity

MAP kinase kinases, MKK3 and **MEKK4**. MKK3 specifically phosphorylates and activates p38, whereas MKK4 phosphorylates and activates both p38 and JNK. Coexpression of MEKK2 or MEKK3 with MKK4 in COS-7 cells resulted in activation of MKK4, as assessed by enhanced autophosphorylation and by its ability to phosphorylate and activate recombinant JNK1 or p38 in vitro. MKK3 autophosphorylation and activation of p38 was also observed following coexpression of MKK3 with MEKK3, but not with MEKK2. Consistent with these observations, immunoprecipitated MEKK2 directly activated recombinant MKK4 in vitro but failed to activate MKK3. The sites of activating phosphorylation in MKK3 and MKK4 were identified within kinase subdomains VII and VIII. Replacement of Ser189 or Thr193 in MKK3 with Ala abolished autophosphorylation and activation of MKK3 by MEKK3. Analogous mutations in MKK4 indicated that Ser221 and, to a lesser extent, Thr225 were necessary for MKK4 activation by MEKK2 and MEKK3. These data indicate that MKK3 is preferentially activated by MEKK3, whereas MKK4 is activated both by MEKK2 and MEKK3. Consistent with these observations, MEKK2 and MEKK3 also activated JNK1 in vivo. However, MEKK3 failed to activate p38 when coexpressed in either the absence or presence of MKK3, indicating that MEKK3 is not coupled to p38 activation in vivo. These observations suggest that regulation of p38 and JNK1 pathways by MEKK3 may involve distinct mechanisms to prevent p38 activation but to allow JNK1 activation.

L2 ANSWER 45 OF 51 MEDLINE DUPLICATE 16

ACCESSION NUMBER: 97236778 MEDLINE
DOCUMENT NUMBER: 97236778 PubMed ID: 9079650
TITLE: Cloning of a novel mitogen-activated protein kinase kinase kinase, **MEKK4**, that selectively regulates the c-Jun amino terminal kinase pathway.
AUTHOR: Gerwins P; Blank J L; Johnson G L
CORPORATE SOURCE: Division of Basic Sciences and Program in Molecular Signal Transduction, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206, USA.
CONTRACT NUMBER: DK 38871 (NIDDK)
DK 48845 (NIDDK)
GM 30324 (NIGMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Mar 28) 272 (13) 8288-95.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U85607; GENBANK-U85608
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970514
Last Updated on STN: 19980206
Entered Medline: 19970502

AB Mitogen-activated protein kinases (MAPKs) are components of sequential kinase cascades that are activated in response to a variety of extracellular signals. Members of the MAPK family include the extracellular response kinases (ERKs or p42/44(MAPK)), the c-Jun amino-terminal kinases (JNKs), and the p38/Hog 1 protein kinases. MAPKs are phosphorylated and activated by MAPK kinases (MKKs or MEKs), which in turn are phosphorylated and activated by MKK/MEK kinases (Raf and MKKK/MEKKs). We have isolated two cDNAs encoding splice variants of a novel MEK kinase, **MEKK4**. The **MEKK4** mRNA is widely expressed in mouse tissues and encodes for a protein of approximately 180 kDa. The **MEKK4** carboxyl-terminal catalytic domain is approximately 55% homologous to the catalytic domains of MEKKs 1, 2, and 3. The amino-terminal region of **MEKK4** has little sequence homology to the previously cloned MEKK proteins. **MEKK4** specifically activates the JNK pathway but not ERKs or p38, distinguishing

it from MEKKs 1, 2 and 3, which are capable of activating the ERK pathway.

MEKK4 is localized in a perinuclear, vesicular compartment similar to the Golgi. **MEKK4** binds to Cdc42 and Rac; kinase-inactive mutants of **MEKK4** block Cdc42/Rac stimulation of the JNK pathway. **MEKK4** has a putative pleckstrin homology domain and a proline-rich motif, suggesting specific regulatory functions different from those of the previously characterized MEKKs.

L2 ANSWER 46 OF 51 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 97449143 MEDLINE
DOCUMENT NUMBER: 97449143 PubMed ID: 9305639
TITLE: A human homolog of the yeast Ssk2/Ssk22 MAP kinase kinase kinases, **MTK1**, mediates stress-induced activation of the p38 and JNK pathways.
AUTHOR: Takekawa M; Posas F; Saito H
CORPORATE SOURCE: Dana-Farber Cancer Institute and Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA.
CONTRACT NUMBER: GM50909 (NIGMS)
GM53415 (NIGMS)
SOURCE: EMBO JOURNAL, (1997 Aug 15) 16 (16) 4973-82.
Journal code: EMB; 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF002715
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 20000303
Entered Medline: 19971017

AB A human homolog of the yeast Ssk2 and Ssk22 mitogen-activated protein kinase kinase kinases (MAPKKK) was cloned by functional complementation of the osmosensitivity of the yeast ssk2delta ssk22delta sho1delta triple mutant. This kinase, termed **MTK1** (MAP Three Kinase 1), is 1607 amino acids long and is structurally highly similar to the yeast Ssk2 and Ssk22 MAPKKKs. In mammalian cells (COS-7 and HeLa), **MTK1** overexpression stimulated both the p38 and JNK MAP kinase pathways, but not the ERK pathway. **MTK1** overexpression also activated the MKK3, MKK6 and SEK1 MAPKKs, but not the MEK1 MAPKK. Furthermore, **MTK1** phosphorylated and activated MKK6 and SEK1 in vitro. Overexpression of a dominant-negative **MTK1** mutant [**MTK1** (K/R)] strongly inhibited the activation of the p38 pathway by environmental stresses (osmotic shock, UV and anisomycin), but not the p38 activation by the cytokine TNF-alpha. The dominant-negative **MTK1** (K/R) had no effect on the activation of the JNK pathway or the ERK pathway. These results indicate that **MTK1** is a major mediator of environmental stresses that activate the p38 MAPK pathway, and is also a minor mediator of the JNK pathway.

L2 ANSWER 47 OF 51 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 18
ACCESSION NUMBER: 1997:654274 CAPLUS
DOCUMENT NUMBER: 127:316115
TITLE: Human mitogen-activated protein kinase kinase 4 as a candidate tumor suppressor
AUTHOR(S): Teng, David H-F.; Perry, William L., III; Hogan, James K.; Baumgard, Michelle; Bell, Russell; Berry, Simin; Davis, Thaylon; Frank, David; Frye, Cheryl; Hattier, Thomas; Hu, Rong; Jammulapati, Srikanth; Janecki, Teresa; Leavitt, Amber; Mitchell, Jeffrey T.; Pero, Ralph; Sexton, David; Schroeder, Marianne; Su, Pi-Hsia; Swedlung, Brad; Kyriakis, John M.; Avruch,

Joseph; Bartel, Paul; Wong, Alexander K. C.; Oliphant, Arnold; Thomas, Alun; Skolnick, Mark H.; Tavtigian, Sean V.
CORPORATE SOURCE: Myriad Genetics, Inc., Salt Lake City, UT, 84108, USA
SOURCE: Cancer Res. (1997), 57(19), 4177-4182
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mitogen-activated protein kinases function in signal transduction path-ways that are involved in controlling key cellular processes in many organisms. A mammalian member of this kinase family, MKK4/JNKK1/SEK1, has been reported to link upstream MEKK1 to downstream stress-activated protein kinase/JNK1 and p38 mitogen-activated protein kinase. This mitogen-activated protein kinase pathway has been implicated in the signal transduction of cytokine- and stress-induced apoptosis in a variety of cell types. Here, we report that 2 human tumor cell lines, derived from pancreatic carcinoma and lung carcinoma, harbor homozygous deletions that eliminate coding portions of the MKK4 locus at 17p, located approx. 10 cM centromeric of p53. In addn., in a set of 88 human cancer cell lines prescreened for loss of heterozygosity, we detected two nonsense and three missense sequence variants of MKK4 in cancer cell lines derived from human pancreatic, breast, colon, and testis cells. In vitro biochem. assays revealed that, when stimulated by MEKK1, four of the five altered MKK4 proteins lacked the ability to phosphorylate stress-activated protein kinase. Thus, the incidence of coding mutations of MKK4 in the set of cell lines is 6 of 213 (.apprx.3%). These findings suggest that MKK4 may function as a suppressor of tumorigenesis or metastasis in certain types of cells.

L2 ANSWER 48 OF 51 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 96288894 MEDLINE
DOCUMENT NUMBER: 96288894 PubMed ID: 8727700
TITLE: Isolation and characterization of two monoclonal antibodies that recognize different epitopes of the human c-kit receptor.
AUTHOR: Morita S; Tsuchiya S; Fujie H; Itano M; Ohashi Y; Minegishi M; Konno T
CORPORATE SOURCE: Department of Pediatric Oncology, Tohoku University, Sendai.
SOURCE: TOHOKU JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Feb) 178 (2) 187-98.
Journal code: VTF; 0417355. ISSN: 0040-8727.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961106
Last Updated on STN: 20000303
Entered Medline: 19961024

AB After immunizing mice with a human megakaryoblastic leukemia cell line, M-MOK, we obtained two monoclonal antibodies which recognize the human c-kit receptor. The monoclonal antibodies, designated **MTK1** and MTK2, were found to specifically recognize Balb/3T3 cells transfected with human c-kit cDNA and not parent Balb/3T3 cells while showing different immunological, biochemical and biological behaviors. Both allowed

visualization of the 140 kDa c-kit protein by Western blot analysis, but **MTK1** detected only positive band with non-reducing conditions for sodium dodecyl sulfate-polyacrylamide gel electrophoresis. **MTK1** partially inhibited the stem cell factor (SCF) induced proliferation of M-MOK cells, whereas, MTK2 was without effect. **MTK1** also inhibited the bone marrow derived colony forming unit granulocyte/macrophage (CFU-GM) formed by granulocyte-macrophage colony stimulating factor (GM-CSF) and SCF. Not only anti-CD34 antibodies (HPCA-1) but also **MTK1** could be shown to concentrate bone marrow CFU-GM and burst forming unit erythroid (BFU-E) effectively. The presently described monoclonal antibodies may therefore be useful for functional analysis of the ligand binding domain of the human c-kit receptor, as well as for further classification of hematopoietic stem cells in addition to the CD34 positive cells.

L2 ANSWER 49 OF 51 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 96145218 MEDLINE
DOCUMENT NUMBER: 96145218 PubMed ID: 8558913
TITLE: Cell surface c-kit receptors in human leukemia cell lines and pediatric leukemia: selective preservation of c-kit expression on megakaryoblastic cell lines during adaptation to in vitro culture.
AUTHOR: Morita S; Tsuchiya S; Fujie H; Itano M; Ohashi Y; Minegishi M; Imaizumi M; Endo M; Takano N; Konno T
CORPORATE SOURCE: Department of Pediatric Oncology, Tohoku University, Sendai, Japan.
SOURCE: LEUKEMIA, (1996 Jan) 10 (1) 102-5.
Journal code: LEU; 8704895. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960312
Last Updated on STN: 20000303
Entered Medline: 19960226

AB We produced a monoclonal antibody **MTK1** which recognized c-kit protein. Using **MTK1**, 31 leukemia cell lines and 76 leukemia blasts from pediatric patients were analyzed for expression of the c-kit receptor by flow cytometry. The c-kit receptor was detectable on four of four cell lines assigned to the megakaryo/erythromegakaryoblastic lineage and on one of seven cell lines of myeloid lineage. C-kit expression was not seen on any of 20 cell lines of erythroid and lymphoid lineages. Furthermore, c-kit was expressed on 16 of 24 nonlymphoid blasts without platelet surface antigens (67%) and on six of eight non-lymphoid blasts with platelet surface antigens (75%), but was not detectable on 44 lymphoid blasts from pediatric leukemia patients. In these cases CD34 was expressed on 26 of 32 myeloid blasts (81%) and on 27 of 44 lymphoid blasts (61%). The findings indicate a dominant expression of the c-kit receptor on established cell lines assigned to the megakaryo/erythromegakaryoblastic lineage, though a high percentage of leukemic myeloblasts also expressed the c-kit receptor on their surface.

L2 ANSWER 50 OF 51 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:183541 CAPLUS
DOCUMENT NUMBER: 120:183541
TITLE: Evidence for a direct hepatotrophic role for insulin in the fetal rat: implications for the impaired hepatic growth seen in fetal growth retardation

AUTHOR(S): Gruppuso, Philip A.; Boylan, Joan M.; Bienieki, Theresa C.; Curran, Thomas R.
CORPORATE SOURCE: Dep. Pediatr., Rhode Island Hosp., Providence, RI, 02903, USA
SOURCE: Endocrinology (1994), 134(2), 769-75
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Perturbations of fetal growth produce parallel but dispropionate changes in fetal liver growth that correlate with circulating fetal insulin concn.

The authors have studied the effects of insulin and two hepatotrophic factors, transforming growth factor-.alpha. (TGF.alpha.) and hepatocyte growth factor (HGF), on DNA synthesis by fetal and adult rat hepatocytes in primary culture. Using serum-free Min. Essential Medium, fetal hepatocytes synthesized DNA without growth factors, unlike adult hepatocytes. Insulin augmented fetal hepatocyte DNA synthesis at 16-24 h in culture. In contrast, TGF.alpha. or HGF maximally stimulated fetal hepatocyte DNA synthesis after 40 h in culture. Insulin and TGF.alpha. were not synergistic in stimulating fetal hepatocyte DNA synthesis, but were synergistic in their action on adult hepatocytes. Brief (10-min) exposure of fetal hepatocytes to TGF.alpha. or HGF, but not insulin, activated **mitogen-activated protein kinase 4**-fold. Prolonged (24-h) exposure to TGF.alpha. or HGF abolished the ability of either to activate mitogen-activated protein kinases, whereas insulin had no effect. Maternal fasting for 48 h before isolation and culturing of fetal hepatocytes abolished the in vitro stimulation of DNA synthesis by insulin without affecting TGF.alpha. action. The authors conclude that insulin has growth-promoting actions on fetal hepatocytes that are distinct and independent from those of TGF.alpha. or HGF.

L2 ANSWER 51 OF 51 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1980:51736 CAPLUS
DOCUMENT NUMBER: 92:51736
TITLE: Antispirochetal effect of two medicated premixes for birds
AUTHOR(S): Stoyanova-Zaikova, L.
CORPORATE SOURCE: Cent. Lab. Control Vet. Preparat., Sofia, Bulg.
SOURCE: Vet.-Med. Nauki (1978), 15(10), 61-7
CODEN: VMDNAV; ISSN: 0506-8215
DOCUMENT TYPE: Journal
LANGUAGE: Bulgarian

AB Addn. of MT3k3 [72059-81-5] (contg. tylosin phosphate, oxytetracycline-HCl, and furazolidone) to the feed of chickens prior to exptl. infection with Borrelia anserina had a good antiospirochetal effect and did not suppress the development of immunity to spirochetosis. A lesser effect was obtained with the related prepn. **MTk1** [72059-80-4], which contained a lower concn. of tylosin and no oxytectracycline. Thus, MT3k3 was recommended for use on poultry farms with outbreaks of spirochetosis.

=> s l2 and (antisens? or RNAi or triplex or ribozym?)

L3 13 L2 AND (ANTISENS? OR RNAI OR TRIPLEX OR RIBOZYM?)

=> d l3 ibib kwic

L3 ANSWER 1 OF 13 MEDLINE
ACCESSION NUMBER: 2002096905 MEDLINE

DOCUMENT NUMBER: 21671319 PubMed ID: 11700306
TITLE: Expression of Galpha 13 (Q226L) induces P19 stem cells to primitive endoderm via MEKK1, 2, or 4.
AUTHOR: Wang Hsien-yu; Kanungo Jyotshnabala; Malbon Craig C
CORPORATE SOURCE: Department of Physiology & Biophysics, University Medical Center, State University of New York, Stony Brook, New York
11794-8661, USA.. wangh@pharm.sunysb.edu
CONTRACT NUMBER: DK30111 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Feb 1) 277 (5) 3530-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020206
Last Updated on STN: 20020420
Entered Medline: 20020228

AB . . . MKK4, and MEKK1 were constitutively activated in clones stably transfected to express Q226L Galpha13. Dominant negative forms of MEKK1 and **MEKK4** were expressed stably in the clones harboring Q226L Galpha13. Expression of dominant negative versions of either MEKK1 or **MEKK4** effectively blocks both the activation of Jun N-terminal kinase as well as the formation of primitive endoderm. Depletion of MEKK1, -2, or -4 by **antisense** oligodeoxynucleotides suppressed signaling from Q226L Galpha13 to JNK1 and primitive endoderm formation. We demonstrate that the signal linkage map from. . .

=> d l3 ibib kwic 2-13

L3 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:256519 CAPLUS
DOCUMENT NUMBER: 136:304039
TITLE: **Antisense** modulation of **MEKK4** expression
INVENTOR(S): Ward, Donna T.; Gaarde, William A.; Monia, Brett P.; Wyatt, Jacqueline R.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002027033	A1	20020404	WO 2001-US30549	20010928

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-676436 A 20000929
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

TI **Antisense** modulation of **MEKK4** expression

AB **Antisense** compds., compns. and methods are provided for modulating the expression of **MEKK4**. The compns. comprise **antisense** compds., particularly **antisense** oligonucleotides, targeted to nucleic acids encoding **MEKK4**. Methods of using these compds. for modulation of **MEKK4** expression and for treatment of diseases assocd. with expression of **MEKK4** are provided.

ST **antisense** oligonucleotide **MEKK4** antiinflammatory antitumor immunol disorder

IT Anti-inflammatory agents
Antitumor agents
Cytotoxic agents
(**antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT Nucleic acids
RNA
mRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT **Antisense** oligonucleotides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT Drug delivery systems
(carriers; **antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT Immunity
(disorder; **antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT 192230-91-4, Mitogen-activated protein kinase kinase 4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**MEKK4**; **antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT 408375-65-5, ISIS 123086 408375-66-6, ISIS 123087 408375-67-7, ISIS 123088 408375-68-8, ISIS 123089 408375-69-9, ISIS 123090
408375-70-2, ISIS 123091 408375-71-3, ISIS 123092 408375-72-4, ISIS 123093 408375-73-5, ISIS 123094 408375-74-6, ISIS 123095
408375-75-7, ISIS 123096 408375-76-8, ISIS 123097 408375-77-9, ISIS 123098 408375-78-0, ISIS 123099 408375-79-1, ISIS 123100
408375-80-4, ISIS 123101 408375-81-5, ISIS 123102 408375-82-6, ISIS 123103 408375-83-7, ISIS 123104 408375-84-8, ISIS 123105
408375-85-9, ISIS 123106 408375-86-0, ISIS 123107 408375-87-1, ISIS 123108 408375-88-2, ISIS 123109 408375-89-3, ISIS 123110
408375-90-6, ISIS 123111 408375-91-7, ISIS 123112 408375-92-8, ISIS 123113 408375-93-9, ISIS 123114 408375-94-0, ISIS 123115
408375-95-1, ISIS 123116 408375-96-2, ISIS 123118 408375-97-3, ISIS 123119 408375-98-4, ISIS 123120 408375-99-5, ISIS 123121
408376-00-1, ISIS 123122 408376-01-2, ISIS 123123 408376-02-3, ISIS 123124 408376-03-4, ISIS 123125 408376-04-5, ISIS 123126
408376-05-6, ISIS 123127 408376-06-7, ISIS 123128 408376-07-8, ISIS 123129 408376-08-9, ISIS 123130 408376-09-0, ISIS 123131
408376-10-3, ISIS 123132 408376-11-4, ISIS 123133 408376-12-5, ISIS 123134 408376-13-6, ISIS 123135 408376-14-7, ISIS 123136
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408376-25-0, ISIS 123147 408376-26-1, ISIS 123148 408376-27-2, ISIS 123149 408376-28-3, ISIS 123150 408376-29-4, ISIS 123151
408376-30-7, ISIS 123152 408376-31-8, ISIS 123153 408376-32-9, ISIS 123154 408376-33-0, ISIS 123155 408376-34-1, ISIS 123156
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123159 408376-38-5, ISIS 123160 408376-39-6, ISIS 123161
408376-40-9, ISIS 123162 409402-00-2 409402-01-3 409402-02-4
409402-03-5 409402-04-6 409402-05-7 409402-06-8 409402-07-9
409402-08-0 409402-09-1 409402-10-4 409402-11-5 409402-12-6
409402-13-7 409402-14-8 409402-15-9 409402-16-0 409402-17-1
409402-18-2 409402-19-3 409402-20-6 409402-21-7 409402-22-8
409402-23-9 409402-24-0 409402-25-1 409402-26-2 409402-27-3
409402-28-4 409402-29-5 409402-30-8 409402-31-9 409402-32-0
409402-33-1 409402-34-2 409402-35-3 409402-36-4 409402-37-5
409402-38-6 409402-39-7 409402-40-0 409402-41-1 409402-42-2
409402-43-3 409402-44-4 409402-45-5 409402-46-6 409402-47-7
409402-48-8 409402-49-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT 109-86-4, 2-Methoxyethanol 554-01-8, 5-Methylcytosine 1463-10-1, 5-Methyluridine 1704-62-7 40615-36-9 58479-61-1 133485-25-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(**antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT 22423-26-3P 163759-49-7P 163759-50-0P 171763-19-2P 182495-98-3P
182495-99-4P 182496-00-0P 182496-01-1P 212061-24-0P 212061-25-1P
212061-26-2P 212061-27-3P 212061-28-4P 212061-29-5P 253145-84-5P
253145-85-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT 163759-94-2P 212061-30-8P 253145-86-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(**antisense** modulation of **MEKK4** expression and treatment of diseases assocd. with expression of **MEKK4**)

IT 408490-51-7 408490-52-8 408490-53-9 408490-54-0 408490-55-1
408490-56-2 408490-57-3 408490-58-4 408490-59-5 408490-60-8
408490-61-9 408490-62-0 408490-63-1 408490-64-2 408490-65-3
408490-66-4 408490-67-5 408490-68-6 408490-69-7 408490-70-0
408490-71-1 408490-72-2 408490-73-3 408490-74-4 408490-75-5
408490-76-6 408490-77-7 408490-78-8 408490-79-9 408490-80-2
408490-81-3 408490-82-4 408490-83-5 408490-84-6 408490-85-7
408490-86-8 408490-87-9 408490-88-0 408490-89-1 408490-90-4
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408491-02-1 408491-03-2 408491-04-3 408491-05-4 408491-06-5
408491-07-6 408491-08-7 408491-09-8 408491-10-1 408491-11-2
408491-12-3 408491-13-4 408491-14-5 408491-15-6 408491-16-7
408491-17-8 408491-18-9 408491-19-0 408491-20-3 408491-21-4
408491-22-5 408491-23-6 408491-24-7 408491-25-8 408491-26-9
408491-27-0 408491-28-1 408491-29-2 408491-30-5 408491-31-6
408491-32-7 408491-33-8 408491-34-9 408491-35-0 408491-36-1
408491-37-2 408491-38-3 408491-39-4
RL: PRP (Properties)
(unclaimed nucleotide sequence; **antisense** modulation of **MEKK4** expression)

L3 ANSWER 3 OF 13 USPATFULL

ACCESSION NUMBER:	2002:105925 USPATFULL
TITLE:	Method and product for regulating apoptosis
INVENTOR(S):	Johnson, Gary L., Boulder, CO, UNITED STATES
PATENT ASSIGNEE(S):	National Jewish Center for Immunology and Respiratory Medicine (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002055130	A1	20020509	
APPLICATION INFO.:	US 2001-858754	A1	20010516	(9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-23130, filed on 13 Feb
1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-39740P	19970214 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Page(s)
LINE COUNT: 6845
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . family of MEKK genes or gene products provided by the present invention apparently consists of at least six different members (**MEKK4**.2 is a splicing varient of **MEKK4**.1 and MEKK2.2 is a sequencing varient of MEKK2) with ample evidence indicating that yet other members of the family exist.

DETD . . . different transcripts by differential splicing. For example, the divergence in sequence amongst the catalytic domains of each of MEKK1 to **MEKK4** indicated that seperate genomic genes encode each paralog. However, MEKK2 and **MEKK4** genes can give rise to at least two different transcripts, presumably be differential splicing.

Expression data suggests that MEKKs 1-4. . .

DETD . . . particularly preferred embodiments MEKK2 and MEKK3 proteins of the present invention have a molecular weight of about 65-75 kD. Preferred **MEKK4** proteins have molecular weights about 180-190 kD. Most preferred molecular weights for the subject MEKKs are: >175 kD (MEKK1), 69.5 kD (MEKK2 or MEKK2.2), 71 kD (MEKK3), 185 kD (**MEKK4**). It is noted that experimental conditions used when running gels to determine the molecular size of putative MEKK proteins will. . . is unclear, but other preferred MEKK1 polypeptides (e.g. MEKK1.2) have apparent molecular weights of about 95-100 kD; and other preferred **MEKK4** polypeptides (e.g., **MEKK4**.2) have apparent molecular weights of about 90-100 kD, more preferably 95-98 kD.

DETD . . . per molecule; (ii) denaturing the double stranded DNA; (iii) renaturing the DNA to form double stranded DNA which can include sense/ **antisense** pairs from different nicked products; (iv) removing single stranded portions from reformed duplexes by treatment with SI nuclease; and (v). . .

DETD . . . of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or **antisense**) and double-stranded polynucleotides.

DETD . . . 620 of MEKK2.1 or 2.2; from about 366 to about 626 of MEKK3; from about 631 to about 890 of **MEKK4**.1; or from about 1338 to about 1597 for **MEKK4**.2.

DETD . . . 360 of MEKK2.1 or 2.2.; from about 1 to about 365 of MEKK3; from about 1 to about 630 of **MEKK4**.1; or from about 1 to about 1337 for **MEKK4**.2.

DETD . . . for example, expression of MEKK proteins by cells. Such therapeutic applications include the use of such oligonucleotides in, for example, **antisense**-, **triplex** formation-, **ribozyme**- and/or RNA drug-based technologies. The present invention, therefore, includes use of such oligonucleotides and methods to interfere with the production. . .

DETD [0119] To further illustrate, another aspect of the invention relates to

the use of the isolated nucleic acid in "**antisense**" therapy. As used herein, "**antisense**" therapy refers to administration or in situ generation of oligonucleotide probes or their derivatives which specifically hybridize (e.g. bind) under. . . the case of binding to DNA duplexes, through specific interactions in the major

groove of the double helix. In general, "**antisense**" therapy refers to the range of techniques generally employed in the art, and includes any therapy which relies on specific. . .

DETD [0120] An **antisense** construct of the present invention can be delivered, for example, as an expression plasmid which, when transcribed in the cell,. . . is complementary to at least a unique portion of the cellular mRNA which encodes a vertebrate MEKK protein. Alternatively, the **antisense** construct is an oligonucleotide probe which is generated ex vivo and which, when introduced into the cell causes inhibition of. . . to endogenous nucleases, e.g. exonucleases and/or endonucleases, and are therefore stable in vivo. Exemplary nucleic acid molecules for use as **antisense** oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Pat. Nos. 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in **antisense** therapy have been reviewed, for example, by Van der Krol et al. (1988) Biotechniques 6:958-976; and Stein et al. (1988). . .

DETD . . . are useful in therapeutic, diagnostic, and research contexts. In therapeutic applications, the oligomers are utilized in a manner appropriate for **antisense** therapy in general. For such therapy, the oligomers of the invention can be formulated for a variety of loads of. . .

DETD [0124] Likewise, the **antisense** constructs of the present invention, by antagonizing the normal biological activity of one of the MEKK proteins, can be used. . .

DETD [0125] Furthermore, the anti-sense techniques (e.g. microinjection of **antisense** molecules, or transfection with plasmids whose transcripts are anti-sense with regard to a MEKK mRNA or gene sequence) can be. . .

DETD . . . MKKs), as MEKI, MEK2, MKK1, MKK2, the stress-activated kinases (SEKs), also known as the Jun kinase kinases (JNKKs), MEKK3 and **MEKK4** or the like. Other downstream targets of the MEKK family can include proteins from the mammalian MAP kinase family which. . .

DETD [0154] In an exemplary embodiment the Ras effector domain or **MEKK4** or **MEKK4**.2 sequence IIGQVCDTPKSYDNVMHVGLR is used to inhibit the interaction of a MEKK protein with a MEKK binding protein.

DETD [0160] For example, as described in the appended examples, overexpression of MEKK1 and MEKK3 (and possibly MEKK2 and **MEKK4**) in certain cells can cause constitutive induction of apoptotic pathways and result in cell death. Accordingly, such recombinant cells can. . .

DETD [0162] In an illustrative embodiment, a portion of **MEKK4** providing a Rac/Cdc42 binding site is provided in one fusion protein, along with a second fusion protein including a Rac/Cdc42 polypeptide. This embodiment of the subject assay permits the screening of compounds which inhibit or potentiate the binding of **MEKK4** and Cdc42.

DETD . . . by a MEKK-dependent pathway, can be, as appropriate, any of the preparations described above, including isolated polypeptides, gene therapy constructs, **antisense** molecules, peptidomimetics or agents identified in the drug assays provided herein.

DETD . . . encode the wild-type form of the protein, or can encode homologs thereof, including both agonists and antagonists, as well as **antisense** constructs. In preferred embodiments, the expression of the transgene is restricted to specific subsets of cells, tissues or developmental stages. . .

DETD . . . which interferes with the expression of a recombinant MEKK gene, such as one which encodes an antagonistic homolog or an **antisense** transcript, can be designed to activate expression of that gene. This interference with expression of the protein can result from. . .

DETD . . . characterized it will be important to characterize their

regulation and interaction with other members of the Ras superfamily. For example, **MEKK4**.1 and 4.2 have been found to bind to Rac/Cdc42 as described herein. Rho, Rac, and Cdc42 are small GTPases that. . .

DETD . . . example of a therapeutic compound of the present invention is the nucleic acid encoding the amino acid residues 1306-1326 of **MEKK4**.2 or 599-619 of **MEKK4**. In other embodiments the peptide or fragments thereof can be used. The Cdc42/Rac binding region of a MEKK peptide (IIGQVCDTPKSYDNVMHVGLR). . .

L3 ANSWER 4 OF 13 USPATFULL

ACCESSION NUMBER:	2002:38558 USPATFULL
TITLE:	Expressed sequences of arabidopsis thaliana
INVENTOR(S):	Gorlach, Jorn, Durham, NC, UNITED STATES An, Yong-Qiang, San Diego, CA, UNITED STATES Hamilton, Carol M., Apex, NC, UNITED STATES Price, Jennifer L., Raleigh, NC, UNITED STATES Raines, Tracy M., Durham, NC, UNITED STATES Yu, Yang, Martinsville, NJ, UNITED STATES Rameaka, Joshua G., Durham, NC, UNITED STATES Page, Amy, Durham, NC, UNITED STATES Mathew, Abraham V., Cary, NC, UNITED STATES Ledford, Brooke L., Holly Springs, NC, UNITED STATES Woessner, Jeffrey P., Hillsborough, NC, UNITED STATES Haas, William David, Durham, NC, UNITED STATES Garcia, Carlos A., Carrboro, NC, UNITED STATES Kricker, Maja, Pittsboro, NC, UNITED STATES Slater, Ted, Apex, NC, UNITED STATES Davis, Keith R., Durham, NC, UNITED STATES Allen, Keith, Cary, NC, UNITED STATES Hoffman, Neil, Chapel Hill, NC, UNITED STATES Hurban, Patrick, Raleigh, NC, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002023280	A1	20020221	
APPLICATION INFO.:	US 2001-770444	A1	20010126	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-178502P	20000127 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	PARADIGM GENETICS, INC, 104 ALEXANDER DRIVE, BUILDING 2, P O BOX 14528, RTP, NC, 277094528
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
LINE COUNT:	3845

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . diagnostic, prophylactic and therapeutic agents employing such novel nucleic acids, their corresponding genes or gene products, including expression constructs, probes, **antisense** constructs, and the like. The genetic sequences may also be used for the genetic manipulation of plant cells, particularly dicotyledonous. . .

SUMM . . . The invention also provides agents employing such novel nucleic acids, their corresponding genes or gene products, including expression constructs, probes, **antisense** constructs, and the like. The nucleotide sequences are provided in the attached SEQLIST.

SUMM [0017] Transgenic plants containing the **antisense** nucleic acids of the invention are useful for identifying other mediators that may induce expression of proteins of interest; for. . .

SUMM . . . of the invention in biological samples, e.g. extracts of cells, to generate additional copies of the nucleic acids, to generate **ribozymes** or **antisense** oligonucleotides, and as single

stranded DNA probes or as triple-strand forming oligonucleotides. The probes described herein can be used to,. . .

SUMM . . . can include promoters attached either at the 5' end of the sense strand or at the 3' end of the **antisense** strand, enhancers, terminators, operators, repressors, and inducers. The promoters can be regulated or constitutive. In some situations it may be. . .

SUMM [0079] **Antisense** nucleic acids are designed to specifically bind to RNA, resulting in the formation of RNA-DNA or RNA-RNA hybrids, with an arrest of DNA replication, reverse transcription or messenger RNA translation. **Antisense** nucleic acids based on a selected nucleic acid sequence can interfere with expression of the corresponding gene. **Antisense** nucleic acids are typically generated within the cell by expression from **antisense** constructs that contain the **antisense** strand as the transcribed strand.

Antisense nucleic acids based on the disclosed nucleic acids will bind and/or interfere with the translation of mRNA comprising a sequence complementary to the **antisense** nucleic acid. The expression products of control cells and cells treated with the **antisense** construct are compared to detect the protein product of the gene corresponding to the nucleic acid upon which the **antisense** construct is based. The protein is isolated and identified using routine biochemical methods.

SUMM . . . expression in specific tissues may be functionally accomplished by introducing a constitutively expressed gene (all tissues) in combination with an **antisense** gene that is expressed only in those tissues where the gene product is not desired. Expression of an **antisense** transcript of this preselected DNA segment in an rice grain, using, for example, a zein promoter, would prevent accumulation of. . .

DETD . . . (MULTICATALYTIC ENDOPEPTIDASE COMPLEX SUBUNIT C5) (TAS-F22|FAFP98) >gi|600387|emb|CAA47753| (X67338) proteosome subunit [Arabidopsis thaliana] Length = 230

414 2027414 5E-37 >gb|AAD25835.1|AC006951_14 (AC006951) **antisense** basic fibroblast growth factor [Arabidopsis thaliana] Length = 283

415 2027415 2E-35 >gb|AAD25553.1|AC005850_10 (AC005850) serine/threonine kinase [Arabidopsis thaliana] Length = 802

416. . .

DETD . . . this gene. [Arabidopsis thaliana] Length = 297

820 2027820 2E-66 >sp|Q39024|MPK4_ARATH MITOGEN-ACTIVATED PROTEIN KINASE HOMOLOG 4 (MAP KINASE 4) (ATMPK4) >gi|2129645|pir.parallel.S40470 **mitogen-activated protein kinase 4** (EC 2.7.1.-) - Arabidopsis thaliana >gi|457400|dbj|BAA04867| (D21840) MAP kinase [Arabidopsis thaliana] Length = 376

821 2027821 Rgd(712-714)

822 2027822 Tyr_Phospho_Site(85-91)

823 2027823 1E-107. . .

L3 ANSWER 5 OF 13 USPATFULL

ACCESSION NUMBER: 2001:235103 USPATFULL

TITLE: Method and product for regulating cell responsiveness to external signals

INVENTOR(S): Johnson, Gary L., Boulder, CO, United States

PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6333170	B1	20011225
APPLICATION INFO.:	US 1996-628829		19960405 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-440421, filed on 12 May 1995, now abandoned Continuation-in-part of Ser. No. US 1994-323460, filed on 14 Oct 1994, now patented, Pat. No. US 5854043 Continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941 , said Ser. No. US 440421

Continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941 , said Ser. No. US 628829 Continuation-in-part of Ser. No. US 1995-410602, filed on 24 Mar 1995, now abandoned

Continuation-in-part of Ser. No. US 1995-472934, filed on 6 Jun 1995, now patented, Pat. No. US 5753446

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Kemmerer, Elizabeth
ASSISTANT EXAMINER: Basi, Nirmal S.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, DeConti, Jr., Esq., Guilio A.,

Lauro, Esq., Peter C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 40 Drawing Figure(s); 30 Drawing Page(s)
LINE COUNT: 6027
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . stringent conditions to a nucleic acid probe having a sequence represented by at least 60 consecutive nucleotides of sense of **antisense** of one or more of SEQ ID NOS: 1, 3, 5, 7, 9, 1 1, or 13. Oligonucleotide probes which. . .

DETD . . . provided by the present invention apparently consists of at least six different members (MEKK 4.2 is a splicing varient of **MEKK4**.1 and MEKK 2.2 is a sequencing varient of MEKK2) with ample evidence indicating that yet other members of the family. . .

DETD . . . NO. 6

MEKK2.2	SEQ ID NO. 7	SEQ ID NO. 8
MEKK3	SEQ ID NO. 9	SEQ ID NO. 10
MEKK4.1	SEQ ID NO. 11	SEQ ID NO. 12
MEKK4.2	SEQ ID NO. 13	SEQ ID NO. 14

DETD . . . MEKK1 to refer to both MEKK1.1 and MEKK 1.2, MEKK 2 to refer to both MEKK2.1 and MEKK 2.2, and **MEKK4** to refer to both **MEKK4**.1 and MEKK 4.2 herein.

DETD . . . different transcripts by differential splicing. For example, the divergence in sequence amongst the catalytic domains of each of MEKK1 to **MEKK4** indicated that seperate genomic genes encode each paralog. However, MEKK2 and **MEKK4** genes can give rise to at least two different transcripts, presumably be differential splicing.

Expression data suggests that MEKKs 1-4. . .

DETD . . . the MEKK catalytic domain with the GTP-bound form of Ras. In addition, it is shown in the appended Examples that **MEKK4** binds to Rac, a low molecular weight GTP binding protein of the Ras superfamily. The sequence of **MEKK4** which binds to Cdc42 and Rac has been identified. This sequence IIGQVCDTPKSYDNVMHVGLR occurrs around residue 1306-1326 of **MEKK4**.2 or 599-619 of **MEKK4** and peptides from this region can be used to block the binding of the MEKK catalytic domain with Cdc42 and. . .

DETD . . . particularly preferred embodiments MEKK2 and MEKK3 proteins of the present invention have a molecular weight of about 65-75 kD. Preferred **MEKK4** proteins have molecular weights about 180-190 kD. Most preferred molecular weights for the subject MEKKs are: >175 kD

(MEKK1), 69.5 kD (MEKK2 or MEKK2.2), 71 kD (MEKK3), 185 kD (**MEKK4**). It is noted that experimental conditions used when running gels to determine the molecular size of putative MEKK proteins will. . . unclear, but other preferred MEKK1 polypeptides (e.g. MEKK 1.2) have apparent molecular weights of about 95-100 kD; and other preferred **MEKK4** polypeptides (e.g., MEKK 4.2) have apparent molecular weights of about 90-100 kD, more preferably 95-98 kD.

DETD . . . per molecule; (ii) denaturing the double stranded DNA; (iii) renaturing the DNA to form double stranded DNA which can include sense/ **antisense** pairs from different nicked products; (iv) removing single stranded portions from reformed duplexes by treatment with S1 nuclease; and (v). . .

DETD . . . of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or **antisense**) and double-stranded polynucleotides.

DETD . . . of MEKK 3; from about 1 to about 630 of MEKK 4.1; or from about 1 to about 1337 for **MEKK4**.2.

DETD . . . for example, expression of MEKK proteins by cells. Such therapeutic applications include the use of such oligonucleotides in, for example, **antisense**-, **triplex** formation-, **ribozyme**- and/or RNA drug-based technologies. The present invention, therefore, includes use of such oligonucleotides and methods to interfere with the production. . .

DETD To further illustrate, another aspect of the invention relates to the use of the isolated nucleic acid in "**antisense**" therapy. As used herein, "**antisense**" therapy refers to administration or in situ generation of oligonucleotide probes or their derivatives which specifically hybridize (e.g. bind) under. . . the case of binding to DNA duplexes, through specific interactions in the major groove of the double helix. In general, "**antisense**" therapy refers to the range of techniques generally employed in the art, and includes any therapy which relies on specific. . .

DETD An **antisense** construct of the present invention can be delivered, for example, as an expression plasmid which, when transcribed in the cell,. . . is complementary to at least a unique portion of the cellular mRNA which encodes a vertebrate MEKK protein. Alternatively, the **antisense** construct is an oligonucleotide probe which is generated ex vivo and which, when introduced into the cell causes inhibition of. . . to endogenous nucleases, e.g. exonucleases and/or endonucleases, and are therefore stable in vivo. Exemplary nucleic acid molecules for use as **antisense** oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Pat. Nos. 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in **antisense** therapy have been reviewed, for example, by Van der Krol et al. (1988) Biotechniques 6:958-976; and Stein et al. (1988). . .

DETD . . . are useful in therapeutic, diagnostic, and research contexts. In therapeutic applications, the oligomers are utilized in a manner appropriate for **antisense** therapy in general. For such therapy, the oligomers of the invention can be formulated for a variety of loads of. . .

DETD Likewise, the **antisense** constructs of the present invention, by antagonizing the normal biological activity of one of the MEKK proteins, can be used. . .

DETD Furthermore, the anti-sense techniques (e.g. microinjection of **antisense** molecules, or transfection with plasmids whose transcripts are anti-sense with regard to a MEKK mRNA or gene sequence) can be. . .

DETD . . . MKKs), as MEK1, MEK2, MKK1, MKK2, the stress-activated kinases (SEKs), also known as the Jun kinase kinases (JNKKs), MEKK3 and **MEKK4** or the like. Other downstream targets of the MEKK family can include proteins from the mammalian MAP kinase family which. . .

DETD In an exemplary embodiment the Ras effector domain or **MEKK4** or **MEKK4**.2 sequence IIGQVCDTPKSYDNVMHVGLR is used to inhibit the interaction of a MEKK protein with a MEKK binding protein.

DETD For example, as described in the appended examples, overexpression of MEKK1 and MEKK3 (and possibly MEKK2 and **MEKK4**) in certain cells can cause constitutive induction of apoptotic pathways and result in cell death. Accordingly, such recombinant cells can. . .

DETD In an illustrative embodiment, a portion of **MEKK4** providing a Rac/Cdc42 binding site is provided in one fusion protein, along with a second fusion protein including a Rac/Cdc42 polypeptide. This embodiment of the subject assay permits the screening of compounds which inhibit or potentiate the binding of **MEKK4** and Cdc42.

DETD . . . Ras as determined by the ability of a Ras effector peptide to block the interaction. In addition, the binding of **MEKK4**. 1 and **MEKK4**.2 to Rac has been localized to the amino acid sequence IIGQVCDTPKSYDNVMHVGLR as described in the appended Examples. Interestingly this sequence. . .

DETD . . . by a MEKK-dependent pathway, can be, as appropriate, any of the preparations described above, including isolated polypeptides, gene therapy constructs, **antisense** molecules, peptidomimetics or agents identified in the drug assays provided herein.

DETD . . . encode the wild-type form of the protein, or can encode homologs thereof, including both agonists and antagonists, as well as **antisense** constructs. In preferred embodiments, the expression of the transgene is restricted to specific subsets of cells, tissues or developmental stages. . .

DETD . . . which interferes with the expression of a recombinant MEKK gene, such as one which encodes an antagonistic homolog or an **antisense** transcript, can be designed to activate expression of that gene. This interference with expression of the protein can result from. . .

DETD . . . a nucleic acid molecule including the kinase catalytic domain of a MEKK protein, for example, MEKK1.1.sub.409-672 MEKK1.sub.1329-1594, MEKK2.1.sub.361-620, MEKK2.2.sub.361-620 MEKK3.sub.366-626, **MEKK4**.1.sub.631-890, **MEKK4**.2.sub.1338-1597. Again, suitable variations of MEKK proteins described herein comprise those proteins encoded by a nucleic acid molecule that are able. . .

DETD . . . the sequence of a MEKK protein which binds to Cdc42 and Rac, such as IIGQVCDTPKSYDNVMHVGLR, occurring around residue 1306-1326 of **MEKK4**.2 or 599-619 of **MEKK4** or mimetics thereof could be used therapeutically. In one embodiment the Rac-binding portion of a MEKK protein or a fragment. . .

DETD . . . characterized it will be important to characterize their regulation and interaction with other members of the Ras superfamily. For example, **MEKK4**.1 and 4.2 have been found to bind to Rac/Cdc42 as described herein. Rho, Rac, and Cdc42 are small GTPases that. . .

DETD . . . example of a therapeutic compound of the present invention is the nucleic acid encoding the amino acid residues 1306-1326 of **MEKK4**.2 or 599-619 of MEKK 4. In other embodiments the peptide or fragments thereof can be used. The Cdc42/Rac binding region. . .

DETD . . . of MEKK 2 and 3. The degenerate primers GA(A/G)(C/T)TIATGGCIGTIAA(A/G)CA (SEQ ID NO: 13) (sense) and TTIGCICC(T/C)TTIAT(A/G)TCIC(G/T)(A/G)TG (SEQ ID NO: 14) (**antisense**) were used in a PCR using first strand cDNA generated from polyadenylated RNA prepared from NIH 3T3 cells. The PCR. . .

DETD . . . were purified, and a second PCR reaction was performed using the first PCR product as template, the MEKK2 or 3 **antisense** oligonucleotide described above and the common sense oligonucleotide encoding a XbaI restriction site, a consensus Kozak initiation site and 17. . .

DETD This Example Demonstrates the Cloning of **MEKK4**.1 and

MEKK4.2, a Splicing Variant of **MEKK4**

DETD . . . TIATGGCIGTIAA(A or G)CA SEQ ID NO: 13 (sense) and TTIGCICC(TorC)TTIAT(A or G)TCIC(G or T_)(A or G)TG SEQ ID NO: 14 (**antisense**) were used in a polymerase chain reaction (PCR) using first strand cDNA generated from polyadenylated RNA prepared from NIH 3T3. . . truncated at the 5'-region and were therefore not full length in the coding region. To obtain the 5' region of **MEKK4** poly RNA was isolated and primers from the partial cDNA used for reverse transcription. cDNAs were generated using the RACE procedure and sequenced. The 5' region of **MEKK4** with upstream in frame stop codons was obtained and ligated to the partial **MEKK4** cDNA to give a full length **MEKK4** cDNA having an open reading frame of 1597 codons.

DETD This Example Demonstrates the Differential Expression of **MEKK4**.2

DETD . . . indicated tissues of a Balb/c mouse, resolved on an agarose gel, transferred to nitrocellulose paper and hybridized with .sup.32 P-labeled **MEKK4**.2 cDNA probe. A single mRNA band approximately 5.8 kb is hybridized with the labeled **MEKK4**.2 probe.

DETD This Example Demonstrates That the **MEKK4** Kinase Domain Activates c-Jun Kinases Activity

DETD COS cells were transfected with pCMV5 expression plasmid encoding no cDNA insert (control), full length **MEKK4** or the truncated **MEKK4** encoding only the catalytic kinase domain. The truncated **MEKK4** kinase domain is consitutitively active when expressed in COS cells. The MEKK1 kinase catalytic domain, and MEKK2 and -3 also. . .

DETD This Example Demonstrates That **MEKK4** Does Not Activate p42/p44 MAP Kinases (ERK1 and ERK2) Activity

DETD COS cells were transfected with pCMV5 expression plasmid encoding no cDNA insert (control), full length **MEKK4**, the truncated **MEKK4** encoding only the catalytic kinase domain or the MEKK1 catalytic domain. The MEKK1 catalytic domain but not the **MEKK4** catalytic domain is capable of activating ERK1 and ERK2 (see FIG. 23).

DETD This Example Demonstrates That **MEKK4** Interacts With Cdc42/Rac

DETD GST fusion proteins encoding Cdc42 or Rac loaded with either GTP.gamma.s or GDP were incubated with **MEKK4** using previously described methods (Russell, M. et al. (1995) J. Biol. Chem. 270:11757-11760). The source of **MEKK4** was either from a Cos cell transient transfection or a recombinant **MEKK4** protein expressed in E. coli. The recombinant **MEKK4** protein was truncated to express residues from 1261-1597 of the full length protein. A GST fusion protein of Ha-Ras was used as a control. The **MEKK4** protein was incubated for 1 hr at 4.degree. C. with either GST-Cdc42, GST-Rac or GST-Ras bound to glutathione-Sepharose beads. Each. . . SDS-Laemmli buffer and resolved by SDS-PAGE using 10% acrylamide gels. The proteins were transferred to nitrocellulose and immunoblotted using a **MEKK4** specific antibody recognizing the extreme COOH-terminus of **MEKK4**. **MEKK4** specifically bound to GST-Cdc42 and GST-Rac in the GTP.gamma.S form. The GDP bound forms of GST-Cdc42 and GST-Rac bound less than 10% of the **MEKK4** bound in the presence of GTP.gamma.s. **MEKK4** did not bind significantly to GST-Ras in either the GTP.gamma.S or GDP bound form.

DETD The sequence IIGQVCDTPKSYDNVHVGLRKV (residues 599-621) of the **MEKK4** sequence set forth as SEQ ID NO: 12)) was synthesized as a GST-fusion protein by standard PCR techniques. The GST-fusion. . .

L3 ANSWER 6 OF 13 USPATFULL

ACCESSION NUMBER: 2001:229388 USPATFULL

TITLE: Expression monitoring of downstream genes in the BRCA1 pathway

INVENTOR(S): Oliner, Jonathan, Mountain View, CA, United States
Christians, Fred, Los Altos, CA, United States

Truong, Vivi, San Jose, CA, United States
Haber, Daniel, Chestnut Hill, MA, United States
Bean, James, Arlington, MA, United States
Miklos, David, W. Roxbury, MA, United States
Harkin, Denis Paul, Knockhill Park, Great Britain

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001051339	A1	20011213
APPLICATION INFO.:	US 2001-808352	A1	20010315 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-203677, filed on 1 Dec 1998, GRANTED, Pat. No. US 6258536
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, WASHINGTON, DC, 20001
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 2842
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . It will be appreciated by one of skill in the art that the direct transcription method described above provides an **antisense** (aRNA) pool. Where **antisense** RNA is used as the target nucleic acid, the oligonucleotide probes provided in the array are chosen to be complementary to subsequences of the **antisense** nucleic acids. Conversely, where the target nucleic acid pool is a pool of sense nucleic acids, the oligonucleotide probes are. . . pool is double stranded, the probes may be of either sense as the target nucleic acids include both sense and **antisense** strands.

DETD [0113] The protocols cited above include methods of generating pools of either sense or **antisense** nucleic acids. Indeed, one approach can be used to generate either sense or **antisense** nucleic acids as desired. For example, the cDNA can be directionally cloned into a vector (e.g., Stratagene's p Bluescript II. . .

DETD . . . this manuscript was in preparation, Takekawa and Saito (1998) reported that GADD45 directly interacts with the upstream regulator of JNK/SAPK, **MEKK4**, leading to activation of JNK/SAPK signaling and apoptosis. Taken together, these observations suggest that BRCA1 may activate JNK/SAPK-dependent apoptosis through. . .

DETD . . . mechanism for its activation of JNK/SAPK-dependent apoptosis, given the very recent observation that GADD45 interacts with and activates the stress-responsive **MTK1**/MEK4 MAPKKK, an upstream regulator of JNK/SAPK, and that overexpression of GADD45 itself triggers apoptosis through JNK/SAPK signaling (Takekawa and Saito,. . .

DETD [0272] Takekawa, M., and Saito, H. (1998) A family of stress-inducible GADD45-llike proteins mediate activation of the stress-responsive **MTK1/MEKK4** MAPKKK Cell95, 521-530.

L3 ANSWER 7 OF 13 USPATFULL
ACCESSION NUMBER: 2001:196837 USPATFULL
TITLE: Human MEKK proteins, corresponding nucleic acid molecules, and uses therefor
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6312934	B1	20011106
	WO 9947686		19990923
APPLICATION INFO.:	US 2000-423890		20000306 (9)

WO 1999-US5556 19990315
20000306 PCT 371 date
20000306 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-78153P	19980316 (60)
	US 1998-99165P	19980904 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Monshipouri, M.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, Lauro, Esq, Peter C., Milasincic, Esq, Debra J.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 35 Drawing Figure(s); 35 Drawing Page(s)
LINE COUNT: 2856
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid molecules encoding human MEKK proteins, and isolated MEKK proteins, are provided. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression. . .

SUMM . . . their kinase domains as well as 65% homology within their catalytic domains. Blank et al., supra. The cloning of murine **MEKK4** revealed approximately 55% homology to the kinase domains of MEKKs 1, 2, and 3 whereas the amino-terminal region of **MEKK4** has little sequence homology to the other MEKK family members. Gerwin et al. (1997) J. Biol. Chem. 272:8288-8295. MEKK1 and **MEKK4**, but not MEKK2 and MEKK3, bind to the low molecular weight GTP-binding proteins Cdc42 and Rac. Furthermore, MEKK1 also binds. . .

DRWD . . . to amino acids 361-619 of SEQ ID NO:10), murine MEKK3 (corresponding to amino acids 367-626 of SEQ ID NO:12), murine **MEKK4** (corresponding to amino acids 1337-1597 of SEQ ID NO:13), human MEKK1 (corresponding to amino acids 1038-1302 of SEQ ID NO:2),. .

.

DETD As used herein, an "**antisense**" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein (e.g., complementary to. . . a double-stranded cDNA molecule, complementary to an mRNA sequence or complementary to the coding strand of a gene. Accordingly, an **antisense** nucleic acid can hydrogen bond to a sense nucleic acid).

DETD Another aspect of the invention pertains to isolated nucleic acid molecules that are **antisense** to the coding strand of a human MEKK MRNA or gene. An **antisense** nucleic acid of the invention can be complementary to an entire human MEKK coding strand, or to only a portion thereof. In one embodiment, an **antisense** nucleic acid molecule is **antisense** to a coding region of the coding strand of a nucleotide sequence encoding human MEKK that is unique to human MEKK (as compared to non-human MEKKs, such as mouse or rat MEKK). In another embodiment, the **antisense** nucleic acid molecule is **antisense** to a noncoding region of the coding strand of a nucleotide sequence encoding human MEKK that is unique to human MEKK (as compared to non-human MEKKs, such as mouse or rat MEKK). In preferred embodiments, an **antisense** of the invention comprises at least contiguous nucleotides of the noncoding strand of SEQ ID NO:1, SEQ ID NO:3, or. . .

DETD . . . 3 to 3908 of SEQ ID NO:1, nucleotides 124-1980 of SEQ ID NO:3, or nucleotides 25-1902 of SEQ ID NO:5), **antisense** nucleic acids of the invention can be designed according to the rules of Watson

and Crick base pairing. The **antisense** nucleic acid molecule may be complementary to the entire coding region of human MEKK mRNA, or alternatively can be an oligonucleotide which is **antisense** to only a portion of the coding or noncoding region of human MEKK mRNA. For example, the **antisense** oligonucleotide may be complementary to the region surrounding the translation start site of human MEKK mRNA. An **antisense** oligonucleotide can be, for example, about 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An **antisense** nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an **antisense** nucleic acid (e.g., an **antisense** oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest, described further in the following subsection).

DETD In another embodiment, an **antisense** nucleic acid of the invention is a **ribozyme**. **Ribozymes** are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. A **ribozyme** having specificity for a human MEKK-encoding nucleic acid can be designed based upon the nucleotide sequence of a human MEKK. . .

DETD . . . further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an **antisense** orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a marner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is **antisense** to human MEKK mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the **antisense** orientation can be chosen which direct the continuous expression of the **antisense** RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of **antisense** RNA. The **antisense** expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which **antisense** nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined. . . by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using **antisense** genes see Weintraub, H. et al., **Antisense** RNA as a molecular tool for genetic analysis, Reviews--Trends in Genetics, Vol. 1(1) 1986.

DETD . . . a DNA target sequence to which ATF 2 binds). Examples of intracellular binding molecules, described in further detail below, include **antisense** human MEKK nucleic acid molecules (e.g., to inhibit translation of human MEKK mRNA), intracellular anti-human MEKK antibodies (e.g., to inhibit. . .

DETD In one embodiment, an inhibitory agent of the invention is an **antisense** nucleic acid molecule that is complementary to a gene encoding human MEKK or to a portion of said gene, or a recombinant expression vector encoding said **antisense** nucleic acid molecule. The use of **antisense** nucleic acids to downregulate the expression of a particular protein in a cell is well known in the art (see e.g., Weintraub, H. et al, **Antisense** RNA as a molecular tool for genetic analysis, Reviews--Trends in Genetics, Vol.

1(1) 1986; Askari, F. K, and McDonnell, W.. . . (1995) Cancer Gene Ther. 2:47-59; Rossi, J. J. (1995) Br. Med. Bull. 51:217-225; Wagner, R.
W. (1994) Nature 372:333-335). An **antisense** nucleic acid molecule comprises a nucleotide sequence that is complementary to the coding strand of another nucleic acid molecule (e.g.,. . . an mRNA sequence) and accordingly is capable of hydrogen bonding to the coding strand of the other nucleic acid molecule. **Antisense** sequences complementary to a sequence of an mRNA can be complementary to a sequence found in the coding region of. . . region and an untranslated region (e.g., at the junction of the 5' untranslated region
and the coding region). Furthermore, an **antisense** nucleic acid can be complementary in sequence to a regulatory region of the gene encoding the mRNA, for instance a transcription initiation sequence or regulatory element. Preferably, an **antisense** nucleic acid is designed so as to be complementary to a region preceding or spanning the
initiation codon on the coding strand or in the 3'untranslated region of
an mRNA. An **antisense** nucleic acid for inhibiting the expression of human MEKK protein in a cell can be designed based upon the nucleotide. . .

DETD An **antisense** nucleic acid can exist in a variety of different forms. For example, the **antisense** nucleic acid can be an oligonucleotide that is complementary to only a portion of a human MEKK gene. An **antisense** oligonucleotides can be constructed using chemical synthesis procedures known in the art. An **antisense** oligonucleotide can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g. phosphorothioate derivatives and acridine substituted nucleotides can be used. To inhibit human MEKK expression in
cells in culture, one or more **antisense** oligonucleotides can be added to cells in culture media, typically at about 200 .mu.g oligonucleotide/ml.

DETD Alternatively, an **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i.e., nucleic acid transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest). Regulatory sequences operatively linked to a nucleic acid cloned in the **antisense** orientation can be chosen which direct the expression of the **antisense** RNA molecule in a cell of interest, for instance promoters and/or enhancers or other regulatory sequences can be
chosen which direct constitutive, tissue specific or inducible expression of **antisense** RNA. For example, for inducible expression of **antisense** RNA, an inducible eukaryotic regulatory system, such as the Tet system (e.g., as described in Gossen,
M, and Bujard, H.. . . et al. (1995) Science 268:1766-1769; PCT Publication No. WO 94/29442; and PCT Publication No. WO 96/01313) can be
used. The **antisense** expression vector is prepared as described above for recombinant expression vectors, except that the cDNA (or portion thereof) is cloned into the vector in the **antisense** orientation. The **antisense** expression vector can be in the form of, for example, a recombinant plasmid, phagemid or attenuated virus. The **antisense** expression vector is introduced into cells using a standard transfection technique, as described above for recombinant expression vectors.

DETD In another embodiment, an **antisense** nucleic acid for use as an inhibitory agent is a ribozvme. **Ribozymes** are catalytic RNA

molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region (for reviews on **ribozymes** see e.g., Ohkawa, J. et al. (1995) J. Biochem. 118:251-258; Sigurdsson, S. T, and Eckstein, F. (1995) Trends Biotechnol. 13:286-289; Rossi, J. J. (1995) Trends Biotechnol. 13:301-306; Kiehntopf, M. et al. (1995) J. Mol. Med. 73:65-71). A **ribozyme** having specificity for human MEKK mRNA can be designed based upon the nucleotide sequence of the human MEKK cDNA. For. . .

DETD . . . goats and sheep. For stimulatory or inhibitory agents that comprise nucleic acids (including recombinant expression vectors encoding human MEKK protein, **antisense** RNA, intracellular antibodies or dominant negative inhibitors), the agents can be introduced into cells of the subject using methods known. . .

DETD . . . 5'-GAACACCATCCAGAAGTTTG-3' (SEQ ID NO:14), which was designed from the mouse MEKK1 (mMEKK1) cDNA sequence, was used in conjunction with the **antisense** primer 5'-CACTTTGTAGACAGGGTCAGC-3' (SEQ ID NO:15) in a polymerase chain reaction (PCR) using the first strand cDNA described above as a. . . to amplify the region from bases 2263-3743, the sense primer 5'-TGGGTCGCCTCTGTCTTATAGACAG-3' (SEQ ID NO:16) was used in conjunction with the **antisense** primer 5'-CACATCCTGTGCTTGGTAAC-3' (SEQ ID NO:17) in a RT-PCR of 30 cycles (1 min. 94.degree. C.; 1 min., 50.degree. C.; 2. . . to amplify the region from bases 580-1310, the sense primer 5'-CGGCCTGGAAGCACGAGTGGT-3' (SEQ ID NO:20) was used in conjunction with the **antisense** primer 5'-TTCATCCTTGATGCTGTTTTC-3' (SEQ ID NO:21) in a RT-PCR of 30 cycles (1 min., 94.degree. C.; 1 min., 50.degree. C.; 2. . .

DETD . . . region of human MEKK2 (hMEKK2), was designed from the mouse MEKK2 (mMEKK2) cDNA sequence, and used in conjunction with the **antisense** primer 5'-TCTGGAATGTATCCTGG-3' (SEQ ID NO:23) in a polymerase chain reaction (PCR) using the first strand cDNA described above as a. . . which annealed to a region that overlapped the previously sequenced portion of hMEKK2, was used in conjunction with the two **antisense** primers 5'-CAGCCAGCTCTCTTCCG-3' (SEQ ID NO:25) and 5'-GGAAAAGTCTTCCGACC-3' (SEQ ID NO:26) in two separate RT-PCR of 30 cycles (1 min, 94.degree.. . . NO:27), which annealed to a region that overlapped the previously sequenced region of hMEKK2, was used in conjunction with the **antisense** primer 5'-GGAGCTGGTGGAGGACCGAAG-3' (SEQ ID NO:28), which annealed to the 3' untranslated region of hMEKK2, in a RT-PCR of 30 cycles. . .

DETD . . . middle of human MEKK3 (hMEKK3), was designed from the mouse MEKK3 (mMEKK3) cDNA sequence and used in conjunction with the **antisense** primer 5'-AGCACGGTCCCGCAGGCAGCC-3) (SEQ ID NO:30). Taq DNA Polymerase (Boehringer Mannheim) was used in a RT-PCR of 30 cycles (1 min,. . . to the 5' untranslated region of hMEKK3, was designed from the mMEKK3 cDNA sequence, and used in conjunction with the **antisense** primer 5'-CTGACAAGGAATTTTCGGCAC-3' (SEQ ID NO:32) which overlapped the previously sequenced portion of hMEKK3, in a RT-PCR of 30 cycles (1. . . a second PCR under the same conditions with the nested sense strand oligo 5'-ACCGCCGCCTCCGCCATCGCC-3' (SEQ ID NO:33) and the nested **antisense** strand oligo 5'-CACTGTTCGCTGGTCTCTGGG-3' (SEQ ID NO:34). A band of approximately 700 bp was isolated from the reaction mixture buffered with. . . NO:35), which annealed to a region that overlapped the previously sequenced region of hMEKK3, was used in conjunction with the **antisense** primer 5'-GCCTGACAGCAGCCCCTTGCC-3' (SEQ ID NO:36), which annealed to the 3' untranslated region of hMEKK3, in a RT-PCR of 30 cycles. . . incubation at 72.degree. C. Subsequently, the nested sense primer 5'-TCCAGTTGCTAAAGAACTTGC-3' (SEQ ID NO:37) was used in conjunction with the nested **antisense** primer 5'-TGGCAGCTGGCAGCCTGATAG-3' (SEQ ID NO:38) in a secondary RT-PCR of 30 cycles (1 min, 94.degree. C.; 1

min, 50.degree. C.;. . .

L3 ANSWER 8 OF 13 USPATFULL

ACCESSION NUMBER:	2001:107621 USPATFULL
TITLE:	Expression monitoring of downstream genes in the BRCA1 pathway
INVENTOR(S):	Oliner, Jonathan, 173 Sierra Vista Ave., Unit 22, Mountain View, CA, United States 94043 Christians, Fred, 1444 Arbor Ave., Los Altos, CA, United States 94024 Truong, Vivi, 7082 Kindra Hill Dr., San Jose, CA, United States 95120 Haber, Daniel, 34 Monadonck Rd., Chestnut Hill, MA, United States 02467 Bean, James, 9 Heath Rd., Arlington, MA, United States 02474 Miklos, David, 61 Oriole St., W. Roxbury, MA, United States 02132 Harkin, Denis Paul, 9 Knockhill Park, Belfast BT5 6HX, Northern Ireland, United Kingdom

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6258536	B1	20010710	
APPLICATION INFO.:	US 1998-203677		19981201	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Fredman, Jeffrey
ASSISTANT EXAMINER:	Chakrabarti, Arun K.
LEGAL REPRESENTATIVE:	Banner & Witcoff, Ltd.
NUMBER OF CLAIMS:	32
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	24 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT:	2762

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD It will be appreciated by one of skill in the art that the direct transcription method described above provides an **antisense** (aRNA) pool. Where **antisense** RNA is used as the target nucleic acid, the oligonucleotide probes provided in the array are chosen to be complementary to subsequences of the **antisense** nucleic acids. Conversely, where the target nucleic acid pool is a pool of sense nucleic acids, the oligonucleotide probes are. . . pool is double stranded, the probes may be of either sense as the target nucleic acids include both sense and **antisense** strands.

DETD The protocols cited above include methods of generating pools of either sense or **antisense** nucleic acids. Indeed, one approach can be used to generate either sense or **antisense** nucleic acids as desired. For example, the cDNA can be directionally cloned into a vector (e.g., Stratagene's p Bluescript II. . .

DETD . . . this manuscript was in preparation, Takekawa and Saito (1998) reported that GADD45 directly interacts with the upstream regulator of JNK/SAPK, **MEKK4**, leading to activation of JNK/SAPK signaling and apoptosis. Taken together, these observations suggest that BRCA1 may activate JNK/SAPK-dependent apoptosis through. . .

DETD . . . mechanism for its activation of JNK/SAPK-dependent apoptosis, given the very recent observation that GADD45 interacts with and activates the stress-responsive **MTK1**/MEK4 MAPKKK, an upstream regulator of JNK/SAPK, and that overexpression of GADD45 itself triggers apoptosis through JNK/SAPK signaling (Takekawa and Saito,. . .

DETD Takekawa, M., and Saito, H. (1998) A family of stress-inducible GADD45-like proteins mediate activation of the stress-responsive **MTK1/MEKK4** MAPKKK Cell 95, 521-530.

L3 ANSWER 9 OF 13 USPATFULL

ACCESSION NUMBER: 2000:74127 USPATFULL
TITLE: MEKK proteins
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center For Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6074861		20000613
APPLICATION INFO.:	US 1995-461145		19950605 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-440421, filed on 12 May 1995 which is a continuation-in-part of Ser. No. US 1995-354516, filed on 21 Feb 1995, now abandoned which is a division of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941, issued on 11 Apr 1995 And a continuation-in-part of Ser. No. US 1994-323460, filed on 14 Oct 1994, now patented, Pat. No. US 5854043 And a continuation-in-part of Ser. No. WO 1994-US11690, filed on 14 Oct 1994 And a continuation-in-part of Ser. No. WO 1994-US4178, filed on 15 Apr 1994 which is a continuation-in-part of Ser. No. US 49254

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Prouty, Rebecca E.,
ASSISTANT EXAMINER: Monshipouri, M.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, DeConti, Jr., Esq., Giulio A., Lauro, Esq., Peter C.
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 44 Drawing Figure(s); 36 Drawing Page(s)
LINE COUNT: 4631
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . U.S. patent application Ser. No. 08/323,460, filed Oct. 14, 1994 discloses nucleic acid and protein sequences for MEKK1, MEKK2, MEKK3, **MEKK4** and MEKK5. In the application, MEKK 1 nucleic acid and protein sequences are represented by SEQ ID NO:1 and SEQ. . .

ID NO:6 refer to MEKK3 nucleic acid and protein sequences, respectively;

SEQ ID NO:7 and SEQ ID NO:8 refer to **MEKK4** nucleic acid and protein sequences, respectively; SEQ ID NO:9 and SEQ ID NO:10 refer to MEKK5 nucleic acid and protein. . .

DETD . . . for example, expression of MEKK proteins by cells. Such therapeutic applications include the use of such oligonucleotides in, for example, **antisense**-, **triplex** formation-, **ribozyme**- and/or RNA drug-based technologies. The present invention, therefore, includes use of such oligonucleotides and methods to interfere with the production. . .

DETD This example describes the isolation of nucleic acid sequences encoding MEKK2, MEKK3 and **MEKK4** protein.

L3 ANSWER 10 OF 13 USPATFULL

ACCESSION NUMBER: 1999:141672 USPATFULL
TITLE: Methods for regulating MEKK protein activity
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5981265		19991109
APPLICATION INFO.:	US 1995-461146		19950605 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-440421, filed on 12 May 1995 which is a continuation-in-part of Ser. No. US

1994-345516, filed on 28 Nov 1994, now abandoned which is a division of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941 And a continuation-in-part of Ser. No. US 1994-323460, filed on 14 Oct 1994 And a continuation-in-part of Ser. No. WO 1994-US11690, filed on 14 Oct 1994, now patented, Pat. No. WO 5854043 And a continuation-in-part of Ser. No. WO 1994-US4178, filed on 15 Apr 1994 which is a continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Spector, Lorraine
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Lauro, Peter C.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 40 Drawing Figure(s); 36 Drawing Page(s)
LINE COUNT: 5111
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . U.S. patent application Ser. No. 08/323,460, filed Oct. 14, 1994 discloses nucleic acid and protein sequences for MEKK1, MEKK2, MEKK3, **MEKK4** and MEKK5. In the application, MEKK 1 nucleic acid and protein sequences are represented by SEQ ID NO:1 and SEQ. . .

ID NO:6 refer to MEKK3 nucleic acid and protein sequences, respectively;

SEQ ID NO:7 and SEQ ID NO:8 refer to **MEKK4** nucleic acid and protein sequences, respectively; SEQ ID NO:9 and SEQ ID NO:10 refer to MEKK5 nucleic acid and protein. . .

DETD . . . for example, expression of MEKK proteins by cells. Such therapeutic applications include the use of such oligonucleotides in, for example, **antisense**-, **triplex** formation-, **ribozyme**- and/or RNA drug-based technologies. The present invention, therefore, includes use of such oligonucleotides and methods to interfere with the production. . .

DETD This example describes the isolation of nucleic acid sequences encoding MEKK2, MEKK3 and **MEKK4** protein.

L3 ANSWER 11 OF 13 USPATFULL
ACCESSION NUMBER: 1998:162314 USPATFULL
TITLE: MEKK-related signal transduction kinases
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5854043		19981229
APPLICATION INFO.:	US 1994-323460		19941014 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Teng, Sally P.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Kara, Catherine J.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 66 Drawing Figure(s); 32 Drawing Page(s)
LINE COUNT: 3248
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example, expression of MEKK proteins by cells. Such therapeutic applications include the use of such oligonucleotides in, for example, **antisense**-, **triplex** formation-, **ribozyme**- and/or RNA drug-based technologies. The present invention, therefore, includes use of such oligonucleotides and methods to interfere with the production. . .

DETD . . . more preferred nucleic acid molecule with which to contact a cell includes a nucleic acid molecule including MEKK1.sub.352-672, MEKK2.sub.352-619, MEKK3.sub.358-626, **MEKK4**.sub.811-1195, MEKK5.sub.863-1247, and combinations thereof. Again, suitable variations of MEKK proteins described herein comprise those proteins encoded by a nucleic acid. . .

L3 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:129769 BIOSIS
DOCUMENT NUMBER: PREV200200129769
TITLE: MyD118/GADD45/CR6 (GADD45b,g,a) modulate blood cell homeostatis & response to genotoxic stress.
AUTHOR(S): Liebermann, Dan A. (1); Amanullah, Arshad (1); Balliet, Arthur (1); Azam, Naiyer (1); Zhang, Wei (1); Hoffman, Barbara (1)
CORPORATE SOURCE: (1) Fels Inst. and Biochemistry, Temple University School of Medicine, Philadelphia, PA USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 79a-80a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB. . . physical interactions, including homologous and heterologous interactions with each other, as well as with other cellular proteins (PCNA, p21, Cdc2, **MTK1**, core histones). Using mice deficient for either MyD118, GADD45a or CR6, or both GADD45a and MyD118, and myeloid differentiation inducible cell lines conditionally expressing GADD45 proteins, or **antisense** oligomers to block GADD45 expression, has provided evidence that GADD45 proteins play a role in regulating homeostasis of hematopoietic tissues. . .

L3 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:289134 BIOSIS
DOCUMENT NUMBER: PREV200100289134
TITLE: MyD118/GADD45/CR6 (GADD45beta,alpha,gamma) in blood cell homeostasis.
AUTHOR(S): Liebermann, Dan A.; Zhang, Wei; Balliet, Arthur; Azam, Naiyer; Vairapandi, Mariappan; Hoffman, Barbara
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 146b. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB. . . physical interactions, including homologous and heterologous interactions with each other, as well as with other cellular proteins (PCNA, p21, Cdc2, **MTK1**, core histones). The combined use of M1 myeloblastic leukemia cells which ectopically express inducible GADD45 proteins, **antisense** oligomers to block their expression, and mice deficient for GADD45 has provided evidence that MyD118/Gadd45/CR6